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Atty. Dkt. No. 041457-0633

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Juan Mantelle et al.
Title:	TRANSDERMAL COMPOSITIONS CONTAINING LOW MOLECULAR WEIGHT DRUGS WHICH ARE LIQUID AT ROOM TEMPERATURES
Appl. No.:	09/986,945
Filing Date:	11/13/2001
Examiner:	Nabila G. Ebrahim
Art Unit:	1618
Confirmation Number:	6420

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
P.O. Box 1450
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Sir:

This is an Appeal under 37 C.F.R. 41.31 stemming from the final Office Action issued July 10, 2008, in the captioned application. A Notice of Appeal was filed October 10, 2008. This Appeal Brief is filed in accordance with 37 C.F.R. § 41.37 together with the appeal fee. If the fee submitted herewith is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741. If a further extension of time is required, Appellant hereby petitions for such extension and authorizes the extension fee to be charged to the same deposit account.

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I. REAL PARTY IN INTEREST

The real party of interest is Noven Pharmaceuticals Inc., the assignee of record of each inventor's entire interest.

II. RELATED APPEALS AND INTERFERENCES

Appellant knows of no prior or pending appeals, judicial proceedings or interferences which are related to, may directly affect, or may be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-26 are currently pending, are finally rejected, and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

No amendments were made after the Non-Final Office Action mailed October 18, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention relates to a transdermal drug delivery system comprising low molecular weight drugs which are liquid at or about room temperatures, and methods for making and using the inventive drug delivery systems. Specification, page 1, lines 18-21. As noted in the specification, transdermal patches having low molecular weight liquids drugs are difficult to formulate because of the tendency of low molecular weight liquid drugs to plasticize the polymer matrix of the transdermal delivery system. Specification, page 3, lines 25-31. The present invention addresses this problem by using a high shear resistant acrylic-based polymer to formulate the transdermal drug delivery system. Specification, page 5, lines 28-31.

The claims on appeal include 6 independent claims: claims 1, 2, 17, 19, 21 and 22.

Independent claim 1 recites a transdermal drug delivery system that comprises a blend of (i) one or more polymers and (ii) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperature. Specification, page 7, lines 29-31. The claimed transdermal system is substantially free of water and liquids having a boiling point below the processing temperatures or equal to or greater than the normal boiling points of the at least one low molecular weight drug. Specification, page 10, lines 36 to page 11, line 3. At least one of the one or more polymers is a high shear resistant acrylic-based pressure-sensitive adhesive polymer having a shear resistance which is greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit. Specification, page 5, lines 36 to page 6, line 3.

Independent claim 2 recites a pressure-sensitive adhesive transdermal drug delivery system that comprises a blend of (i) one or more solvent based high shear resistant acrylic-based polymers which have a shear resistance greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit (specification, page 5, lines 36 to page 6, line 3, page 12, lines 10-12 and page 22, lines 20-24) and (ii) a therapeutically effective amount of one or more drugs, at least one of which has a molecular weight of less than about 300 daltons and is a liquid at or about room temperature (specification, page 7, lines 29-31 and page 19, lines 3-5). The claimed pressure-sensitive adhesive transdermal drug delivery system forms a

polymer matrix which has sufficient tack and shear to remain in place under conditions of use. Specification, page 22, lines 13-20.

Independent claim 17 recites a method for producing a pressure-sensitive transdermal drug delivery system suitable for transdermal delivery of a drug. Specification, page 17, lines 35-20. The inventive method comprises producing a blend of (a) one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance of greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit and (b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures. Specification, page 5, lines 36 to page 6, line 3 and page 7, lines 29-31. The method further comprises forming the blend into a polymer matrix, and drying the polymer matrix to remove the solvent system so as to form a transdermal drug delivery system, wherein the polymer matrix has sufficient tack and shear for application to a human being. Specification, page 12, lines 28-34.

Independent claim 19 recites a pressure-sensitive adhesive transdermal drug delivery system that comprises a blend of (a) a pressure-sensitive adhesive polymer consisting of one or more solvent-based high shear resistant acrylic-based polymers that have a shear resistance greater than or equal to 50 hours at 4 pounds per square inch and 72° Fahrenheit (specification, page 5, lines 36-37) and (b) a therapeutically effective amount of one or more drugs, at least one of which has a molecular weight of less than about 300 daltons and is a liquid at or about room temperature (specification, page 7, lines 29-31 and page 19, lines 3-5). The claimed transdermal drug delivery system forms a polymer matrix which has sufficient tack and shear to remain in place under conditions of use. Specification, page 22, lines 13-20.

Independent claim 21 recites a method for producing a pressure-sensitive transdermal drug delivery system that comprises producing a blend of (a) a pressure-sensitive adhesive polymer consisting of one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance greater than or equal to 50 hours at 4 pounds per square inch and 72° Fahrenheit and mixtures thereof and (b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less

than about 300 daltons and is liquid at or about room temperatures. Specification, page 5, lines 36-37 and page 7, lines 29-31. The claimed method also comprises forming the blend into a polymer matrix, and drying the polymer matrix to remove the solvent system so as to form a transdermal drug delivery system, wherein the polymer matrix has sufficient tack and shear for application to a human being. Specification, page 12, lines 28-34.

Independent claim 22 recites a method for producing a pressure-sensitive transdermal drug delivery system suitable for the transdermal delivery of a drug. Specification, page 17, lines 35-20. The inventive method comprises producing a blend of (a) one or more solvent-based high shear resistant acrylic-based polymers and (b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures. Specification, page 6, lines 9-11, page 7, lines 29-31 and page 19, lines 3-5. The method also comprises forming the blend into a polymer matrix, and drying the polymer matrix to remove the solvent system so as to form a transdermal drug delivery system, wherein the polymer matrix has sufficient tack and shear for application to a human being. Specification, page 12, lines 28-34.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are as follows:

(i) The rejection of claim 1 and dependent claims 24-26 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the phrase "below processing temperatures."

(ii) The rejection of claims 1 and 5 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the phrase "equal to or greater than the normal boiling points of the at least one low molecular weight drug."

(iii) The rejection of claims 1-6 and 10-21 under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 93/00058 ("Miranda").

(iv) The rejection of claims 1-5, 7, 8, 10, 12, and 14-21 under 35 U.S.C. § 102(b) as allegedly being anticipated by EP0524776 ("Pfister"). Independent claims 1, 19, 21, 22, and their dependent claims are argued separately.

(v) The rejection of claims 1-23 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pfister in view of U.S. Patent No. 5,284,660 ("Lee") and U.S. Patent No. 5,230,898 ("Hortsman"). Independent claims 1, 19, 21, 22 and their dependent claims are argued separately.

VII. ARGUMENT

a. The Claims Satisfy 35 U.S.C. §112, Second Paragraph

i. The Proper Standard For Definiteness

The requirement for definiteness is embodied in 35 U.S.C. 112, second paragraph. As explained in the MPEP "compliance with the requirement for definiteness is whether the claim meets the threshold requirements of clarity and precision, and not whether more suitable language or modes of expression are available". MPEP § 2173.02. The test for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, (Fed. Cir. 1986). Thus, if one skilled in the art is able to ascertain the meaning of the terms in light of the specification, the requirement for definiteness under 35 U.S.C. 112, second paragraph, is satisfied.

ii. Claim 1 Is Definite

Claim 1 and the claims that depend therefrom (claims 24-26) are rejected for alleged indefiniteness for reciting liquids having a boiling point "below processing temperatures." This rejection is improper and should be reversed for at least the following reasons.

The phrase "below processing temperatures" in claim 1 would be readily understood by a skilled artisan. As taught in the specification, methods of making transdermal systems are well-known in the art, and involve, for example, forming a blend of the components and heating (drying) to remove solvents and form the transdermal system. Specification, paragraph bridging pages 10-11. A person skilled in the art making a transdermal drug delivery system readily would know the processing temperatures being used. Thus, this phrase does not refer to an unknown parameter, but one that would be readily known when the invention is practiced. A skilled artisan, therefore, would find nothing indefinite about the recitation of liquids having a boiling point "below processing temperatures." Moreover, boiling points of the components used to make transdermal systems are known in the art, published in reference books, and provided by suppliers. Thus, a skilled artisan could readily know whether a system is substantially free of liquids having a boiling point below such

processing temperatures, as recited in claim 1. Accordingly, the claims are definite without reciting a specific temperature, as required by the Examiner.

iii. Claims 1 and 5 Are Definite

Claim 1 and 5 are rejected for alleged indefiniteness for reciting liquids having a boiling point "equal to or greater than the normal boiling points of the at least one low molecular weight drug." This rejection is improper and should be reversed for at least the following reasons.

The phrase "equal to or greater than the normal boiling points of the at least one low molecular weight drug" would be understood by a skilled artisan to mean liquids having a boiling point equal to or greater than the normal boiling points of the at least one low molecular weight drug being formulated. A person skilled in the art formulating a transdermal system with at least one low molecular weight drug would know (or could readily determine) the normal boiling point of the selected drug(s), and so readily could ensure that the system is substantially free of liquids having a boiling point equal to or greater than the normal boiling points of the selected low molecular weight drug(s). Thus, the claims do not need to recite specific drugs or their normal boiling points in order to satisfy the definiteness requirements of §112.

b. The Claimed Invention Is Novel

i. Miranda Does Not Anticipate The Claimed Invention

Claims 1-6 and 10-21 are rejected as allegedly being anticipated by WO/9300058 ("Miranda"). Specifically, the Examiner states that Miranda teaches a transdermal system wherein a blend of polymers is used to affect the rate of drug delivery from the composition. The Examiner further asserts that Miranda's transdermal system should exhibit the same shear resistance as that recited by the claims because the disclosed transdermal system has the "same compounds" (*i.e.*, an acrylate polymer) as claimed. To support the rejection, the Examiner has relied on the doctrine of "inherency," asserting that same compounds should

have the same properties. This conclusion is incorrect, however, for at least the reasons stated below, and thus should be reversed by the Board.

Miranda does not teach a polymer blend that has at least one high-shear resistant polymer. Moreover, Miranda fails to disclose that its acrylic-based polymers are high shear resistant polymers, much less that they have a shear resistance greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit or having a shear resistance "which is greater than or equal to 50 hours at 4 pounds per square inch and 72° Fahrenheit, as recited in the instant claims. Miranda also provides no teaching or suggestion to use a high shear resistant acrylic-based polymer in a transdermal system with a low molecular weight drug, as recited in claims 1-6 and 10-21. In fact, the Examiner has failed to identify a single acrylic-based polymer disclosed in Miranda that has the shear resistant characteristics recited in the claims.

To establish inherency

> the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

MPEP § 2112. The evidence of record does not support the rejection.

Miranda discloses compositions which may include acrylic-based polymers such as Duro-Tak 80-1194, Duro-Tak 80-1196, and Duro-Tak 80-1197. However, none of these acrylic based polymers have a shear resistance as set forth in the claims.

The data sheets in the evidence appendix show that both Duro-Tak 80-1194 and Duro-Tak 80-1196 have a shear resistance of only 15 hours at 8 pounds per square inch and 72°

Fahrenheit, and Duro-Tak 80-1197 has a shear resistance of >24 hours at 4 pounds per square inch and 72° Fahrenheit. *See* Duro-Tak 87-2194 Data Sheet (for Duro-Tak 80-1194, since renamed 87-2194); Duro-Tak 87-2196 Data Sheet (for Duro-Tak 80-1196, since renamed 87-2196); and Duro-Tak 80-1057 Data Sheet (for Duro-Tak 80-1197, now discontinued but in the same family as Duro-Tak 80-1057) (copies attached). Thus, the specific acrylic-based polymers listed in Miranda do not inherently anticipate the polymers recited in the pending claims.

The Examiner's decision to maintain the § 102(b) rejection despite this evidence is improper and should be reversed.

ii. Pfister Does Not Anticipate The Claimed Invention

Claims 1-5, 7, 8, 10, 12, and 14-21 are rejected as allegedly being anticipated by EP 0524776 ("Pfister"). Specifically, the Examiner states that Pfister discloses a blend of polysiloxane and polyacrylate to form an adhesive that is useful as a transdermal drug delivery device. The Examiner is of the opinion that because Pfister discloses adding a polyacrylate having a molecular weight of 1,000,000 to 4,000,000, it is expected that such a polymer will have shear resistance values that overlap the values recited in the claims. The Examiner has misinterpreted the Pfister reference, however, and so Applicants respectfully request that the Board reverse this rejection.

Pfister discloses silicone-based pressure sensitive adhesive compositions that are used for the transdermal delivery of drugs. Pfister specifically mentions that when silicone pressure-sensitive adhesives are formulated with or come in contact with drugs, solvents, excipients, or skin penetration enhancers, the silicone pressure-sensitive adhesive can be plasticized which results in a loss of tack, adhesiveness and a resistance to flow. *See* Pfister at page 2, lines 16-19. To remedy this problem, Pfister suggests adding a cohesive strengthening agent to its polysiloxane based pressure-sensitive adhesive. An example of such a filler is the polyacrylate "carbomer" cited by the Examiner. Pfister at page 5, line 25-28. This filler is used to increase the cohesive strength of Pfister's silicone-based pressure

sensitive adhesive and so does not read on the recited "high shear resistant acrylic-based polymer" as claimed.

The Office Action also argues that "Table C2" allegedly provides evidence of inherency of the recited shear resistance because the values in Table C2 are allegedly "within the range of the instant claims." Office Action, page 5. However, this is a misrepresentation of Table C2. Page 14 of Pfister describes the shear of the entire adhesive composition, which includes the silicone pressure sensitive adhesive and a cohesive strengthening agent. Pfister does not describe the shear resistance of the individual polymers, let alone that of the acrylic carbomer. Accordingly, Pfister does not teach a composition comprising an acrylic-based polymer with a shear resistance of 50 hours at 8 pounds per square inch at 72° Fahrenheit or 50 hours at 4 pounds per square inch at 72° Fahrenheit, as claimed.

For at least these reasons, Applicant respectfully requests the Board to reverse this rejection.

iii. Claims 1 and 22 & Dependent Claims 24-26 Are Separately Patentable over Pfister

Claim 1 recites a transdermal drug delivery system having at least one high shear resistant acrylic-based pressure-sensitive adhesive polymer, while claim 22 recites a method for producing a pressure-sensitive transdermal system using such a polymer. The Office Action cites the carbomer of Pfister as reading on the acrylic-based polymer recited in the instant claims. However, the carbomer of Pfister is not a "pressure sensitive-adhesive," as recited in claims 1 and 22. Thus claims 1 and 22 and their dependents, claims 24-26, are separately patentable over Pfister.

iv. Claims 19 and 21& Dependent Claim 20 Are Separately Patentable over Pfister

Claim 19 recites a pressure-sensitive transdermal drug delivery system comprising a pressure-sensitive adhesive polymer which "consists of one or more solvent based high shear resistant acrylic-based polymers." Claim 21 recites a method for producing a pressure-

sensitive transdermal system using such a polymer. Pfister is directed to silicone-based pressure-sensitive adhesives to which may be added a cohesive strengthening agent, such as a polyacrylate carbomer. Because Pfister does not teach or suggest a pressure-sensitive adhesive polymer which "consists of" acrylic-based polymers, claims 19 and 21 and dependent claim 20 are separately patentable over Pfister.

c. The Claimed Invention Is Not Obvious

i. The Proper Standard For Obviousness:

The requirement for non-obviousness is embodied in 35 U.S.C. § 103, which provides in pertinent part that:

A patent may not be obtained ... "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill....". *See, e.g. In re Kotzab,* 217 F.3d 1365, 1375 (Fed. Cir. 2000).

In a recent Supreme Court decision addressing the appropriate standard for obviousness (*KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (U.S. 2007)), the Court explained that the proper question for evaluating obviousness is "whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR*, 127 S.Ct. at 1741. Here, where no combination of the prior art leads to the present invention, the obviousness rejections are improper, and should be reversed.

ii. *Pfister, Lee & Hortsman Do Not Suggest The Invention*

Claims 1-5, 7, 8, 10, 12, and 14-21 are rejected as allegedly being unpatentable over EP 0524776 ("Pfister"), in view of U.S. Patent No. 5,284,660 ("Lee") and further in view of U.S. Patent No. 5,230,898 ("Horstman"). The Examiner opines that Lee remedies the deficiency of Pfister by teaching the relative amount of drug recited in claim 6 (1-40% by weight of the dry weight of the transdermal system). Office Action at page 6. The Examiner cites Horstman for teaching a transdermal drug delivery device comprising amphetamine, as

recited by claim 23. The combined teachings of the cited references fail to suggest the claimed invention, however.

As shown above, Pfister fails to suggest a transdermal drug delivery system as recited in the independent claims. Neither Lee nor Hortsman, which are cited for teaching specific elements of the dependent claims, remedy the deficiencies of Pfister. Thus, the § 103 rejection is improper and should be reversed.

iii. Claims 1 and 22 & Dependent Claims 24-26 Are Separately Patentable over Pfister

As shown above, claims 1 and 22 and dependent claims 24-26 are separately patentable over Pfister, because Pfister does not teach or suggest an acrylic-based pressure-sensitive adhesive polymer as recited in these claims. Lee and Hortsman do not remedy the deficiencies of Pfister in this regard.

iv. Claims 19 and 21& Dependent Claim 20 Are Separately Patentable over Pfister

As shown above, claims 19 and 21 and dependent claim 20 are separately patenable over Pfister because Pfister does not teach or suggest a pressure-sensitive adhesive polymer that consists of one or more solvent based high shear resistant acrylic-based polymers, as recited in these claims. Lee and Hortsman do not remedy the deficiencies of Pfister in this regard.

d. Conclusion

For at least the foregoing reasons the pending rejections are improper and should be reversed.

Respectfully submitted,

Date December 8, 2008

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VIII. CLAIMS APPENDIX

1. A transdermal drug delivery system comprising a blend of:

(a) one or more polymers; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures,

wherein said system is substantially free of water and liquids having a boiling point (i) below processing temperatures and (ii) equal to or greater than the normal boiling points of the at least one low molecular weight drug; and,

wherein at least one of said one or more polymers is a high shear resistant acrylic-based pressure-sensitive adhesive polymer having a shear resistance which is greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit.

2. A pressure-sensitive adhesive transdermal drug delivery system suitable for transdermal drug delivery comprising a blend of:

(a) one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance which is greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures, wherein the transdermal drug delivery system forms a polymer matrix which has sufficient tack and shear to remain in place under conditions of use.

3. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the one or more high shear resistant acrylic-based polymers have a shear resistance which is greater than or equal to 100 hours at 4 pounds per square inch and 72° Fahrenheit.

4. A pressure-sensitive transdermal drug delivery system as claimed in claim 3, wherein the one or more high shear resistant acrylic-based polymers have a shear resistance which is greater than or equal to 100 hours at 8 pounds per square inch and 72° Fahrenheit.

5. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the system is substantially free of water and liquids having a normal boiling point below processing temperatures and also about equal to or greater than the normal boiling points of the one or more low molecular weight drugs.

6. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the one or more drugs are present in a range of 1 to 40 weight percent, based on the dry weight of the total transdermal system.

7. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the one or more high shear resistant acrylic-based polymers have a weight average molecular weight in the range of about 600,000 to about 1,000,000 daltons.

8. A pressure-sensitive transdermal drug delivery system as claimed in claim 7, wherein the one or more high shear resistant acrylic-based polymers have a weight average molecular weight in the range of about 700,000 to about 900,000 daltons.

9. A pressure-sensitive transdermal drug delivery system as claimed in claim 8, wherein the one or more high shear resistant acrylic-based polymers have a weight average molecular weight in the range of about 750,000 to about 850,000 daltons.

10. A pressure-sensitive transdermal drug delivery system for transdermal drug delivery as claimed in claim 2, wherein the one or more drugs comprise nicotine.

11. A pressure sensitive transdermal drug delivery system as claimed in claim 10, wherein said nicotine is present in its free-base or free-acid form.

12. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the one or more acrylic-based polymers comprise a pressure-sensitive adhesive.

13. A pressure-sensitive transdermal drug delivery system as claimed in claim 12, wherein the one or more high shear resistant, acrylic-based polymers are present in the system in a range of about 10-90 weight per cent, based on the dry weight of the total transdermal system.

14. A pressure-sensitive transdermal drug delivery system as claimed in claim 2 further comprising a backing material superimposed on one surface of the blend, the backing material being substantially impermeable to the drug contained therein.

15. A pressure-sensitive transdermal drug delivery system as claimed in claim 14 further comprising a release liner superimposed on a surface of the blend opposite the backing material.

16. A pressure-sensitive transdermal drug delivery system as claimed in claim 2, wherein the system further comprises an additive selected from one or more of a filler, an enhancer and an excipient.

17. A method of producing a pressure-sensitive transdermal drug delivery system suitable for a transdermal drug delivery system, comprising the steps of:

(1) producing a blend of:

(a) one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance of greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit and mixtures thereof; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures, wherein the blend is in a solvent system;

(2) forming the blend into a polymer matrix; and

(3) drying the polymer matrix to remove the solvent system to form the transdermal drug delivery system, wherein the system forms a polymer matrix which has sufficient tack and shear for application to a human being.

18. A method as claimed in claim 17, wherein the high shear resistant polymer comprises a high molecular weight pressure-sensitive acrylic-based polymer.

19. A pressure-sensitive adhesive transdermal drug delivery system suitable for transdermal drug delivery comprising a blend of:

(a) a pressure-sensitive adhesive polymer which consists of one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance which is greater than or equal to 50 hours at 4 pounds per square inch and 72° Fahrenheit; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures, wherein the transdermal drug delivery system forms a polymer matrix which has sufficient tack and shear to remain in place under conditions of use.

20. A pressure-sensitive adhesive transdermal drug delivery system as claimed in claim 19, wherein the one or more solvent-based high shear resistant acrylic-based polymers have a shear resistance which is greater than or equal to 50 hours at 8 pounds per square inch and 72° Fahrenheit.

21. A method of producing a pressure-sensitive transdermal drug delivery system suitable for a transdermal drug delivery system, comprising the steps of:

(1) producing a blend of:

(a) a pressure-sensitive adhesive polymer which consists of one or more solvent-based high shear resistant acrylic-based polymers having a shear resistance of greater than or equal to 50 hours at 4 pounds per square inch and 72° Fahrenheit and mixtures thereof; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures, wherein the blend is in a solvent system;

(2) forming the blend into a polymer matrix; and

(3) drying the polymer matrix to remove the solvent system to form the transdermal drug delivery system, wherein the system forms a polymer matrix which has sufficient tack and shear for application to a human being.

22. A method of producing a pressure-sensitive transdermal drug delivery system suitable for a transdermal drug delivery system, comprising the steps of:

(1) producing a blend of:

(a) one or more polymers, wherein at least one of said one or more polymers is a solvent-based high shear resistant acrylic-based pressure-sensitive adhesive polymer; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is a low molecular weight drug with a molecular weight of less than about 300 daltons and is liquid at or about room temperatures, wherein the blend is in a solvent system;

(2) forming the blend into a polymer matrix; and

(3) drying the polymer matrix to remove the solvent system to form the transdermal drug delivery system, wherein the system forms a polymer matrix which has sufficient tack and shear for application to a human being.

23. A pressure-sensitive transdermal drug delivery system for transdermal drug delivery as claimed in claim 2, wherein the one or more drugs comprise amphetamine.

24. A pressure-sensitive transdermal drug delivery system for transdermal drug delivery as claimed in claim 1, wherein the one or more drugs comprise nicotine.

25. A pressure sensitive transdermal drug delivery system as claimed in claim 24, wherein said nicotine is present in its free-base or free-acid form.

26. A pressure-sensitive transdermal drug delivery system for transdermal drug delivery as claimed in claim 1, wherein the one or more drugs comprise amphetamine.

IX. EVIDENCE APPENDIX

(1) WO 93/00058, first cited by Appellant in an Information Disclosure Statement dated December 12, 2002.

(2) EP 0524776, first cited by the Examiner in the Office Action dated June 7, 2006.

(3) U.S. Patent No. 5,284,660, first cited by the Examiner in the Office Action dated June 7, 2006.

(4) Product sheet for Duro-Tak 80-1057, first submitted by Appellant with the response to the Non-Final Office Action dated October 18, 2007.

(5) Product sheet for Duro-Tak 87-2196, first submitted by Appellant with the response to the Non-Final Office Action dated October 18, 2007.

(6) Product sheet for Duro-Tak 87-2194, first submitted by Appellant with the response to the Non-Final Office Action dated October 18, 2007.

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(54) Title: SOLUBILITY PARAMETER BASED DRUG DELIVERY SYSTEM AND METHOD FOR ALTERING DRUG SATURATION CONCENTRATION

(57) Abstract

The method of adjusting the saturation concentration of a drug in a transdermal composition for application to the dermis, which comprises mixing polymers having differing solubility parameters, so as to modulate the delivery of the drug. This results in the ability to achieve a predetermined permeation rate of the drug into and through the dermis. In one embodiment, a dermal composition of the present invention comprises a drug, an acrylate polymer, and a polysiloxane. The dermal compositions can be produced by a variety of methods known in the preparation of drug-containing adhesive preparations, including the mixing of the polymers, drug, and additional ingredients in solution, followed by removal of the processing solvents. The method and composition of this invention permit selectable loading of the drug into the dermal formulation and adjustment of the delivery rate of the drug from the composition through the dermis, while maintaining acceptable shear, tack, and peel adhesive properties.

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SOLUBILITY PARAMETER BASED DRUG DELIVERY SYSTEM AND METHOD FOR ALTERING DRUG SATURATION CONCENTRATION

Background of the Invention

This invention relates generally to transdermal drug delivery systems, and more particularly, to a transdermal drug delivery composition wherein a blend of polymers is utilized to affect the rate of drug delivery from the composition. More specifically, a plurality of polymers having differing solubility parameters, preferably immiscible with each other, adjusts the solubility of the drug in a polymeric adhesive system formed by the blend and modulates the delivery of the drug from the composition and through the dermis.

The use of a transdermal composition, for example a pressure-sensitive adhesive containing a medicament, namely, a drug, as a means of controlling drug delivery through the skin at essentially a constant rate, is well known. Such known delivery systems involve incorporation of a medicament into a carrier such as a polymeric matrix and/or a pressure-sensitive adhesive formulation. The pressure-sensitive adhesive must adhere effectively to the skin and permit migration of the medicament from the carrier through the skin and into the bloodstream of the patient.

Many factors influence the design and performance of sustained or controlled release drug delivery products, and dermal delivery systems in general, including drug properties, optimum delivery rate, target site(s), type of therapy (short-term or chronic), patient compliance, etc. Among the drug properties which are known to influence the rate of release or permeation, or both, into the skin are the physicochemical properties, including molecular size, shape, and volume; solubility (both in the delivery

system and through the skin); partitioning characteristics; degree of ionization; charge; and protein binding propensity.

When a drug is contained in a carrier, for example, a pressure-sensitive adhesive for transdermal delivery, the rate of administration may be affected by the rate of release of the drug from the carrier, as well as the rate of passage of the drug through the skin. These rates vary from drug-to-drug and from carrier-to-carrier. A variety of mathematical equations have been proposed in the prior art to describe theoretically the fundamentals of mass transfer phenomena involved in diffusion through a carrier and development of a flux across a membrane such as the skin.

Transdermal drug delivery systems can be divided into two general groups: system-controlled and skin-controlled devices. With skin-controlled devices, net drug delivery is controlled by the rate of drug permeation through the skin. Skin-controlled systems can be further subdivided into monolithic devices and reservoir devices.

Generally, a monolithic system comprises a drug dispersed or dissolved in a matrix comprising a homogeneous polymeric material of, illustratively, silicone adhesive, silicone rubber, acrylic adhesive, polyethylene, polyisobutylene, polyvinyl chloride, nylon, or the like. The drug is dissolved in the polymeric matrix until its saturation concentration is reached. Any additional drug remains dispersed within the matrix. As drug is removed from the surface of the matrix, more of the drug diffuses out of the interior in response to the decreased concentration at the surface. The release rate is therefore not constant over time, but instead gradually decreases as the drug concentration decreases.

The flux, or percutaneous absorption rate of drugs through the skin, is described by Fick's first law of diffusion:

$$J = -D(dC_m/dx),$$

where J is the flux in g/cm^2/sec, D is the diffusion coefficient of the drug through the skin in cm^2/sec, and dC_m/dx is the concentration gradient of active agent across the skin.

In order to modify the rate of delivery from a monolithic transdermal device and into the dermis, the prior art has typically focused on selecting a specific single-polymer matrix or a blend of soluble (miscible) polymers. Illustrative examples are the novel polymers described in U.S. Patent Nos. 4,898,920 and U.S. 4,751,087. There is a need in the art to modify the rate of delivery while using commercially available polymer components.

Another common technique for modifying the rate of drug delivery is the addition of a vehicle or enhancer to the formulation to increase the solubility of the drug within the polymer matrix, for example by adding a co-solvent such as a polyhydric alcohol or by changing the skin permeability, for example by adding enhancers such as ethanol. There is a further need to be able to modulate the delivery of a drug from a polymer matrix without adding vehicles or enhancers.

There is no example in the prior art of using a simple blend of adhesive polymers to affect the rate of drug delivery from a monolithic adhesive-based transdermal composition. However, U.S. Patent No. 4,814,168, granted March 21, 1989, and a continuation-in-part thereof, U.S. Patent No. 4,994,267, issued on February 19, 1991, both assigned to Noven Pharmaceuticals, Inc., Miami, FL, disclose the use of a multipolymer, specifically an ethylene/vinyl acetate

copolymer or an ethylene/vinyl acetate/acrylic terpolymer, a rubber and a tackifier in a carrier composition to improve the adhesive properties. The composition of U.S. Patent No. 4,994,267 further includes an acrylate polymer in the system for additional improvement to the adhesive properties.

Drug concentration in a monolithic transdermal delivery device can vary widely depending on the drug and polymers used. For example, certain drugs are effective in low doses and therefore the transdermal formulation may involve low concentrations, illustratively 5% or less by weight of the medicament in an adhesive. Other drugs, such as nitroglycerin, require large doses to be effective and the transdermal formulation therefore may involve high drug concentrations, approximately between 5 to 40% or more by weight in an adhesive. Low concentrations of medicament typically do not critically affect the adhesion, tack, and shear resistance properties of the adhesive. However, low drug concentrations in the adhesive can result in difficulties in achieving an acceptable delivery rate of the medicament. High concentrations, on the other hand, frequently affect the adhesion properties of the adhesives. The deleterious effects are particularly exacerbated by drugs which also act as plasticizersor solvents for the polymeric adhesive material (*e.g.*, nitroglycerin in polyacrylates).

There is a need in the art for an adhesive composition for transdermal delivery systems which can selectably incorporate low concentrations of drug and deliver same at an adequate and controlled rate or incorporate high concentrations of drugs while retaining good physical adhesive properties.

It is, therefore, an object of this invention to provide a transdermal drug delivery system wherein the

rate of drug delivery from the transdermal composition may be selectably modulated.

It is another object of this invention to provide a transdermal drug delivery system wherein the rate of drug delivery from the transdermal composition may be selectably modulated by adjusting the solubility and/or diffusivity of the drug in the multiple polymer adhesive system.

It is also an object of this invention to provide a transdermal drug delivery system wherein the multiple polymer adhesive system is simple to manufacture.

It is a further object of this invention to provide a transdermal drug delivery system wherein drug-loading of a multiple polymer adhesive system may be selectably varied without adverse effects on drug delivery rate and adhesive properties, such as adhesion, tack, and shear resistance.

It is additionally an object of this invention to provide a transdermal drug delivery system wherein a novel multiple polymer adhesive system is provided which has desirable physical properties.

Summary of Invention

The foregoing and other objects are achieved by this invention which provides a transdermal drug delivery system wherein a blend of at least two polymers having differing solubility parameters adjusts the solubility of a drug in the polymeric blend and thereby modulates the delivery of the drug from the system and through the dermis.

In accordance with a composition aspect of the invention, an improved pressure-sensitive adhesive composition of the type which is suitable as a matrix for controlled release of a bioactive agent therefrom comprises a blend of a first polymeric adhesive material having a first solubility parameter and a

second polymeric adhesive material having a second solubility parameter, the first and second solubility parameters being different from one another. The blend, therefore, has a characteristic net solubility parameter. In embodiments incorporating a bioactive agent in the improved pressure-sensitive adhesive composition, the characteristic net solubility parameter can be preselected to adjust the saturation concentration of a bioactive agent in the composition and thereby control the release of the bioactive agent. The saturation concentration of the bioactive agent may be adjusted either upward or downward depending upon whether the rate of release is to be enhanced or retarded.

In preferred embodiments, the bioactive agent may comprise a drug. In particularly, preferred embodiments, the drug is a steroid, such as an estrogen or a progestational agent, or combination thereof. In other preferred embodiments, the drug may be a β_2-adrenergic agonist, such as albuterol, or a cardioactive agent, such as nitroglycerin. In still other embodiments, the bioactive agent is a cholinergic agent, such as pilocarpine, or an antipsychotic such as haloperidol or a tranquilizer/sedative such as alprazolam.

The pressure-sensitive adhesive composition may further include enhancers, fillers, co-solvents, and excipients as are known in the art for use in such compositions.

In a preferred embodiment of the improved pressure-sensitive adhesive, the first polymeric adhesive material is a polyacrylate and the second adhesive material is a polysiloxane. The polyacrylate is preferably present in the pressure-sensitive adhesive composition in an amount ranging from about

2-96% by weight and the polysiloxane is present in an amount ranging from about 98-4%. Preferably, the ratio of polyacrylate to polysiloxane is from about 2:98 to about 96:4, and more preferably from about 2:98 to about 86:14 by weight.

In a dermal adhesive composition embodiment of the invention, a multiple polymer adhesive system consisting essentially of a blend of 2-96% by weight of an acrylate polymer and 98-4% by weight of a polymer of siloxane, the multiple polymer adhesive system being in an amount of about 99-50% by weight of the dermal adhesive composition. This is combined with a bioactive agent in the amount of 0.3-50% by weight of the total dermal adhesive composition. Optional additives, such as co-solvent for the bioactive agent (up to 30% by weight) and enhancers (up to 20% by weight) may be included in the dermal adhesive composition.

In a transdermal drug delivery device embodiment, the improved pressure-sensitive adhesive of the present invention is combined with a drug. The transdermal drug delivery device may comprise a monolithic adhesive matrix device in some embodiments. Of course, the transdermal drug delivery device may include a backing material and a release liner as is known in the art.

The saturation concentration of a drug in a transdermal drug delivery device of the type having a drug-containing pressure-sensitive adhesive diffusion matrix is adjusted in accordance with a method aspect of the present invention by blending at least two polymers having differing solubility parameters to form a pressure-sensitive adhesive diffusion matrix having a net solubility parameter which modifies the delivery rate of the a drug from the pressure-

sensitive adhesive diffusion matrix and through the dermis.

Brief Description of the Drawing

Comprehension of the invention is facilitated by reading the following detailed description, in conjunction with the annexed drawing, in which:

FIG. 1 is a schematic illustration of a monolithic transdermal drug delivery device of the present invention;

FIG. 2 is a graphic representation of the steady-state nitroglycerin flux rates through cadaver skin *in vitro* from a transdermal drug delivery composition of the present invention (formulation of Example 1) and two commercially-available nitroglycerin-containing transdermal delivery devices: Transderm-Nitro® (a trademark of Ciba-Geigy Corporation, Summit, NJ), and Nitro-Dur® (a trademark of Key Pharmaceuticals, Inc., Kenilworth, NJ);

FIG. 3 is a graphical representation which summarizes *in vitro* nitroglycerin flux results through cadaver skin for the polymeric systems of Examples 2-5. The composition of Example 2 (polyacrylate-only adhesive) is compared to the multiple polymer compositions of Examples 3, 4, and 5, in which the polyacrylate is blended with a polyethylene vinyl acetate, a polyisobutylene, and a polysiloxane, respectively;

FIG. 4 is a graphical representation of the steady-state nitroglycerin flux through cadaver skin *in vitro* from a multiple polymer transdermal adhesive system of Example 6 comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 5 is a graphical representation of steady-state estradiol flux through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone

and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 6 is a graphical representation of average estradiol flux through cadaver skin *in vitro* from 0 to 22 hours and from 22 to 99 hours for a multiple polymer transdermal adhesive system comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 7 is a graphical representation of steady-state norethindrone acetate flux through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 8 is a graphical representation of average estradiol and norethindrone acetate flux through cadaver skin *in vitro* for a multiple polymer transdermal adhesive system comprising both drugs and various weight ratios of polyacrylate and polysiloxane;

FIG. 9 is a graphical representation showing the ratio of average estradiol to norethindrone acetate flux (estradiol flux divided by norethindrone acetate flux) through cadaver skin *in vitro* for a multiple polymer transdermal adhesive system comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 10 is a graphical representation of steady-state flux of pilocarpine through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 11 is a graphical representation of steady-state albuterol and nitroglycerin flux through cadaver

skin *in vitro* from multiple polymer transdermal adhesive systems (polyacrylate/polysiloxane) of the present invention (Examples 24 - 27), and Nitro-Dur®, respectively;

FIG. 12 is a graphical representation of steady-state estradiol flux through cadaver skin *in vitro* from two different multiple polymer transdermal adhesive systems polyacrylate/ polysiloxane and polyacrylate/polybutylene;

FIGS. 13 and 14 show the relationship of flux rate (J) plotted against apparent diffusion coefficient (D) and net solubility parameter (SP), respectively, for Compositions I-VI of Example 6. The net solubility parameter, SP_{net}, was calculated using a weighted average of the solubility parameters of the individual polymers comprising the matrix:

$$SP_{net} = \O_{ps}SP_{ps} + \O_{pa}SP_{pa},$$

where $\O_{ps}$ is the weight percentage of polysiloxane and SP_{ps} is the solubility parameter of polysiloxane. The subscript "pa" refers to the polyacrylate; and

FIG. 15 is a plot of diffusion coefficient versus net solubility parameter.

Detailed Description

In one aspect of the present invention, a pressure-sensitive adhesive composition is provided which comprises a blend of at least two polymers. The blend of at least two polymers is herein referred to as a multiple polymer adhesive system. The term "blend" is used herein to mean that there is no, or substantially no, chemical reaction or cross-linking (other than simple H-bonding) between the polymers in the multiple polymer adhesive system.

In another aspect of the invention, a controlled release dermal composition comprises a drug, or other bioactive agent, in combination with the multiple

polymer adhesive system. In this aspect, the multiple polymer adhesive not only functions as a carrier matrix for the drug, but enhances the rate of release of the drug, and hence the transdermal permeation rate. In some embodiments of the invention, however, the multiple polymer adhesive system will function to retard the transdermal permeation rate.

The invention is premised on the discovery that the transdermal permeation rate of a drug from the multiple polymer adhesive system can be selectively modulated by adjusting the solubility of the drug in the device. As used herein, the term "transdermal permeation rate" means the rate of passage of the drug through the skin; which, as known in the art, may or may not be affected by the rate of release of the drug from the carrier.

The polymers comprising the multiple polymer adhesive system are inert to the drug, and are preferably immiscible with each other. Forming a blend of multiple polymers results in an adhesive system having a characteristic "net solubility parameter," the selection of which advantageously permits a selectable modulation of the delivery rate of the drug by adjusting the solubility of the drug in the multiple polymer adhesive system.

Solubility parameter, also referred to herein as "SP", has been defined as the sum of all the intermolecular attractive forces, which are empirically related to the extent of mutual solubility of many chemical species. A general discussion of solubility parameters is found in an article by Vaughan, "Using Solubility Parameters in Cosmetics Formulation," J. Soc. Cosmet. Chem., Vol.36, pages 319-333 (1985). Many methods have been developed for the determination of solubility parameters, ranging from theoretical calculations to totally empirical

correlations. The most convenient method is Hildebrand's method, which computes the solubility parameter from molecular weight, boiling point and density data, which are commonly available for many materials and which yields values which are usually within the range of other methods of calculation:

$$SP = (\Delta E_v/V)^{1/2},$$

where V = molecular weight/density and ΔE_v = energy of vaporization.

Alternatively written, $SP = (\Delta H_v/V - RT/V)^{1/2}$ where ΔH_v = heat of vaporization, R = gas constant, and T is the absolute temperature, °K. For materials, such as high molecular weight polymers, which have vapor pressures too low to detect, and thus for which ΔH_v is not available, several methods have been developed which use the summation of atomic and group contributions to ΔH_v:

$$\Delta Hv = \Sigma_i \Delta h_i,$$

where Δh_i is the contribution of the ith atom or group to the molar heat of vaporization. One convenient method has been proposed by R. F. Fedors, Polymer Engineering and Science, Vol. 14, p. 147 (1974). In this method ΔE_v and V are be obtained by simply assuming that

$\Delta Ev = \Sigma_i \Delta e_i$ and $V = \Sigma_i v_i$, where Δe_i and v_i are the additive atomic and group contributions for the energy of vaporization and molar volume, respectively.

Yet another method of calculating the solubility parameter of a material is described by Small, J. Applied Chem. Vol. 3, p. 71 (1953).

Table I-A below sets forth solubility parameters of some exemplary adhesive polymers which would be useful in the practice of the invention and shows the variation of SP with molecular weight, free -OH and -COOH groups, the degree of cross-linking. Table IA is

in $(cal/cm^3)^{1/2}$ and $(J/cm^3)^{1/2}$ as calculated by Small's method.

TABLE IA

Polymers	Solubility Parameter $(cal/cm^3)^{1/2}$	$(J/cm^3)^{1/2}$
Addition polymers of unsaturated esters		
Polymethyl methacrylate	9.3	19.0
Polyethylmethacrylate	9.1	18.6
Polymethylacrylate	9.7	19.8
Polyethylacrylate	9.2	18.8
Hydrocarbon polymers		
Polyethylene	8.1	16.6
Polystyrene	9.1	18.6
Polyisobutylene	7.7	15.7
Polyisoprene	8.1	16.6
Polybutadiene	8.4	16.6
Polyethylene/butylene	7.9	16.2
Halogen-containing polymers		
Polytetrafluoroethylene	6.2	12.7
Polyvinylchloride	9.5	19.4
Polyvinylidene chloride	12.2	24.9
Polychloroprene	9.4	19.2
Polyacrylonitrile	12.7	26.0
Condensation polymers		
Nylon -6.6	13.6	27.8
Epon resin 1004 (epoxy)	9.7	19.8
Polysiloxanes		
Polydimethylsiloxane	7.3	14.9
Copolymers		
Polybutadiene-co-acrylonitrile: 75/25 to 70/30	9.25	18.9
Polybutadiene-co-styrene: 75/25 to 72/28	8.5	17.4

excerpted from Kraton® Thermoplastic Rubber Shell Chemical Co. Product Brochure Number SC: 198-89

Table I-B below sets forth solubility parameters calculated by Fedors' method and are expressed in units of $(J/cm^3)^{1/2}$.

TABLE I-B

Components	Solubility Parameter, $(J/cm^3)^{1/2}$
polyethylene/vinyl acetate (40% VAc)	20.9
polydimethylsiloxane	15.1
polyisobutylene	17.6
polyethylene	17.6
polyethyl methacrylate	19.8
polyethyl acrylate	20.9
polymethyl acrylate	21.7
polymethyl methacrylate	22.3
polystyrene	22.5
nitroglycerin	27.0
estradiol	24.5
norethindrone acetate	21.3
pilocarpine	22.9
albuterol	26.7

In accordance with the principles of the invention, the transdermal permeation rate is controlled by varying the polymer components of the multiple polymer adhesive system so as to alter the difference in the solubility parameter of the multiple polymer adhesive system relative to that of the drug (see Examples 2-5, or 28 and 29, hereinbelow). Preferably the solubility parameters of the polymer components are different from one another by an increment of at least 2 $(J/cm^3)^{1/2}$. Most preferably they differ by at least 4 $(J/cm^3)^{1/2}$.

The transdermal permeation rate is also controlled by varying the relative proportions of the polymers comprising the multiple polymer adhesive system (see Example 6 hereinbelow).

The multiple polymer adhesive system is preferably formulated so that it is a pressure-sensitive adhesive at room temperature and has other desirable characteristics for adhesives used in the transdermal drug delivery art; such characteristics include good adherence to skin, ability to be peeled or otherwise removed without substantial trauma to the

skin, retention of tack with aging, *etc.* In general, the multiple polymer adhesive system should have a glass transition temperature (T_g), measured using a differential scanning calorimeter, of between about -70° C to 0° C.

Selection of the particular polymer composition is governed in large part by the drug to be incorporated in the device, as well as the desired rate of delivery of the drug. Those skilled in the art can readily determine the rate of delivery of drugs from the multiple polymer transdermal adhesive system in order to select suitable combinations of polymers and drug for a particular application. Various techniques can be used to determine the rate of delivery of the drug from the polymer. Illustratively, the rate of delivery can be determined by measuring the transfer of drug from one chamber to another through cadaver skin over time, and calculating, from the obtained data, the drug delivery or flux rate.

In a particularly preferred embodiment of the invention, the multiple polymer adhesive system comprises a blend of an acrylic pressure-sensitive adhesive and a silicone pressure-sensitive adhesive. The acrylic-based polymer and silicone-based polymer are preferably in a ratio by weight, respectively, from about 2:98 to about 96:4, more preferably from about 2:98 to about 90:10, and even more preferably about 2:98 to about 86:14. The amount of acrylic-based polymer (hereinafter referred to broadly as a polyacrylate) and silicone-based polymer (hereinafter referred to broadly as a polysiloxane) is selected to modify the saturation concentration of the drug in the multiple polymer adhesive system in order to affect

the rate of delivery of the drug from the system and through the skin.

The adjustment to the saturation concentration of the drug in the multiple polymer adhesive system can either be an increase or a decrease. It has been found that when a polyacrylate having a solubility parameter SP of about 21 $(J/cm^3)^{1/2}$ is used as the principal polymer of a nitroglycerin (SP about 27 $(J/cm^3)^{1/2}$) monolithic system, a significant increase in the transdermal permeation rate of nitroglycerin can be achieved by the addition of a polymer having a lower solubility parameter, for example a polysiloxane (SP about 15 $(J/cm^3)^{1/2}$). By reducing the "net" solubility parameter of the multiple polymer transdermal adhesive system, the difference between the solubility parameter of nitroglycerin and the multiple polymer adhesive system is increased. This increased solubility parameter difference, results in a lower saturation concentration for nitroglycerin, and thereby a greater thermodynamic driving force. Conversely, the composition of the multiple polymer adhesive system can be selected so that the saturation concentration of the drug in the system is increased, so the rate of delivery is retarded, such as would be desirable for administration of scopolamine.

Advantageously, the method and composition of the present invention permit selectable loading of the drug in the transdermal drug delivery system. The concentration by weight of the drug in the dermal composition is preferably about 0.3 to about 50 percent, more preferably about 0.5 to about 40 percent, and even more preferably about 1.0 to about 30 percent. Irrespective of whether there is high-loading or low-loading of the drug into the dermal composition, the multiple polymer adhesive system of

the present invention can be formulated to maintain acceptable shear, tack, and peel adhesive properties.

Although not wishing to be bound by theory, particularly in this case where the structure of the composition has not been analyzed, it is postulated that the polymers of varying solubility parameters, for example, the polysiloxane and the polyacrylate, result in a heterogenous mix, with the components of the polymeric mixture performing as a mutually interpenetrating polymeric network in the composition. In other words, the multiple polymer adhesive system is a mixture of essentially mutually insoluble or immiscible polymers, in contradistinction to the typical prior art transdermal drug delivery systems derived from a single polymer or a solution of mutually soluble polymers.

In the practice of the preferred embodiment of the invention, the acrylic-based polymer can be any of the homopolymers, copolymers, terpolymers, and the like of various acrylic acids. In such preferred embodiments, the acrylic-based polymer constitutes preferably from about 2% to about 95% of the total weight of the total dermal composition, and preferably 2% to about 90%, and more preferably about 2% to about 85%, the amount of acrylate polymer being dependent on the amount and type of drug used.

The acrylate polymers of this invention are polymers of one or more monomers of acrylic acids and other copolymerizable monomers. The acrylate polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. By varying the amount of each type of monomer added, the cohesive properties of the resulting acrylate polymer can be changed as is known in the art. In general, the acrylate polymer is composed of at least 50% by

weight of an acrylate or alkyl acrylate monomer, from 0 to 20% of a functional monomer copolymerizable with the acrylate, and from 0 to 40% of other monomers.

Acrylate monomers which can be used include acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, and tridecyl methacrylate.

Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which can be used include acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate.

Further details and examples of acrylic adhesives which are suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Suitable acrylic adhesives are commercially available and include the polyacrylate adhesives sold under the trademarks Duro-Tak 80-1194, Duro-Tak 80-1196, and Duro-Tak 80-1197 by National Starch and Chemical Corporation, Bridgewater, New Jersey.

Suitable polysiloxanes include silicone pressure-sensitive adhesives which are based on two major components: a polymer, or gum, and a tackifying

resin. The polysiloxane adhesive is usually prepared by cross-linking the gum, typically a high molecular weight polydiorganosiloxane, with the resin, to produce a three-dimensional silicate structure, via a condensation reaction in an appropriate organic solvent. The ratio of resin to polymer is the most important factor which can be adjusted in order to modify the physical properties of polysiloxane adhesives. Sobieski, *et al.*, "Silicone Pressure Sensitive Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Further details and examples of silicone pressure sensitive adhesives which are useful in the practice of this invention are described in the following U.S. Patents: 4,591,622; 4,584,355; 4,585,836; and 4,655,767.

Suitable silicone pressure-sensitive adhesives are commercially available and include the silicone adhesives sold under the trademarks BIO-PSA X7-3027, BIO-PSA X7-4919, BIO-PSA X7-2685, and BIO-PSA X7-3122 by Dow Corning Corporation, Medical Products, Midland, Michigan. BIO-PSA-3027 is particularly suitable for use in formulations containing amine-functional drugs, such as albuterol.

In the practice of a preferred embodiment of the invention, the polysiloxane constitutes preferably from about 4% to about 97% of the total weight of the total dermal composition, and preferably about 8% to about 97%, and more preferably about 14% to about 97%.

In practicing the invention, any bioactive agent may be included in the dermal composition. Illustratively the bioactive agent is a drug. Any drug which is capable of producing a pharmacological response, localized or systemic, irrespective of whether therapeutic, diagnostic, or prophylactic in

nature, in plants or animals is within the contemplation of the invention. In addition to drugs, bioactive agents such as pesticides, insect repellents, sun screens, cosmetic agents, *etc.* are within the contemplation of the invention. It should be noted that the bioactive agents may be used singly or as a mixture of two or more such agents, and in amounts sufficient to prevent, cure, diagnose or treat a disease, as the case may be.

Exemplary active drugs that can be administered by the novel transdermal drug delivery system of this invention include, but are not limited to:

1. Cardioactive medications, illustratively, organic nitrates such as nitroglycerin, isosorbide dinitrate, and isosorbide mononitrates; quinidine sulfate; procainamide; thiazides such as bendroflumethiazide, chlorothiazide, and hydrochlorothyazide; nifedipine; nicardipine; adrenergic blocking agents, such as timolol and propranolol; verapamil; diltiazem; captopril; clonidine and prazosin.

2. Androgenic steroids, such as testosterone, methyltestosterone and fluoxymesterone.

3. Estrogens, such as conjugated estrogens, esterified estrogens, estropipate, 17β estradiol, 17β-estradiol valerate, equilin, mestranol, estrone, estriol, 17β-ethinyl estradiol, and diethylstilbestrol.

4. Progestational agents, such as progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

5. Drugs having an action on the central nervous system, for example sedatives, hyponotics, antianxiety agents, analgesics and anesthetics, such as chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, and nicotine.

6. Nutritional agents, such as vitamins, essential amino acids and essential fats.

7. Anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.

8. Antihistamines, such as diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, and chlorpheniramine.

9. Respiratory agents, such as theophilline and β_2-adrenergic agonists such as albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, and tetroquinol.

10. Sympathomimetics, such as dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine and epinephrine.

11. Miotics, such as pilocarpine, and the like.

12. Cholinergic agonists, such as choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.

13. Antimuscarinic or muscarinic cholinergic blocking agents such as atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, and eucatropine.

14. Mydriatics, such as atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine and hydroxyamphetamine.

15. Psychic energizers such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

16. Anti-infectives, such as antibiotics, including penicillin, tetracycline, chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; antibacterials, such as erythromycin and clarithromycin; and other anti-infectives including nitrofurazone and the like.

17. Dermatological agents, such as vitamins A and E.

18. Humoral agents, such as the prostaglandins, natural and synthetic, for example PGE_1, $PGE_2\alpha$, and $PGF_2\alpha$, and the PGE_1 analog misoprostol.

19. Antispasmodics, such as atropine, methantheline, papaverine, cinnamedrine, and methscopolamine.

20. Antidepressant drugs, such as isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, and trazodone.

21. Anti-diabetics, such as insulin, and anti-cancer drugs such as tamoxifen and methotrexate.

22. Anorectic drugs, such as dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, and phentermine.

23. Anti-allergenics, such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and pheniramine.

24. Tranquilizers, such as reserpine, chlorpromazine, and antianxiety benzodiazepines such as alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

25. Antipsychotics, such as thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone.

26. Decongestants, such as phenylephrine, ephedrine, naphazoline, tetrahydrozoline.

27. Antipyretics, such as aspirin, salicylamide, and the like.

28. Antimigrane agents, such as dihydroergotamine and pizotyline.

29. Drugs for treating nausea and vomiting, such as chlorpromazine, perphenazine, prochlorperazine, promethazine, triethylperazine, triflupromazine, and trimeprazine.

30. Anti-malarials, such as the 4-aminoquinolines, α-aminoquinolines, chloroquine, and pyrimethamine.

31. Anti-ulcerative agents, such as misoprostol, omeprazole, and enprostil.

32. Peptides, such as growth releasing factor.

33. Drugs for Parkinson's disease, spasticity, and acute muscle spasms, such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, and dantrolene.

34. Anti-estrogen or hormone agents, such as tamoxifen or human chorionic gonadotropin.

The active agents can be present in the composition in different forms, depending on which form yields the optimum delivery characteristics. Thus, in the case of drugs, the drug can be in its free base or acid form, or in the form of salts, esters, or any other pharmacologically acceptable derivatives, or as components of molecular complexes.

The amount of drug to be incorporated in the composition varies depending on the particular drug, the desired therapeutic effect, and the time span for which the device is to provide therapy. For most drugs, the passage of the drugs through the skin will be the rate-limiting step in delivery. Thus, the amount of drug and the rate of release is typically selected so as to provide transdermal delivery characterized by a zero order time dependency for a prolonged period of time. The minimum amount of drug in the system is selected based on the amount of drug which passes through the skin in the time span for which the device is to provide therapy. Normally, the amount of drug in the system can vary from about 0.3% to about 50% by weight, and preferably, for the lower

drug doses permitted by this invention, from about 1.0% to about 30%.

Of course, the composition of the transdermal drug delivery system can also contain agents known to accelerate the delivery of the drug through the skin. These agents have been referred to as skin-penetration enhancers, accelerants, adjuvants, and sorption promoters, and are collectively referred herein as "enhancers." This class of agents includes those with diverse mechanisms of action including those which have the function of improving the solubility and diffusibility of the drug within the multiple polymer and those which improve percutaneous absorption, for example, by changing the ability of the stratum corneum to retain moisture, softening the skin, improving the skin's permeability, acting as penetration assistants or hair-follicle openers or changing the state of the skin including the boundary layer. Some of these agents have more than one mechanism of action, but in essence they serve to enhance the delivery of the drug.

Some examples of enhancers are polyhydric alcohols such as dipropylene glycol, propylene glycol, and polyethylene glycol which enhance drug solubility; oils such as olive oil, squalene, and lanolin; fatty ethers such as cetyl ether and oleyl ether; fatty acid esters such as isopropyl myristate which enhance drug diffusibility; urea and urea derivatives such as allantoin which affect the ability of keratin to retain moisture; polar solvents such as dimethyldecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetonide, dimethylsulfoxide, decylmethylsulfoxide, and dimethylformamide which affect keratin permeability; salicylic acid which softens the keratin; amino acids which are penetration

assistants; benzyl nicotinate which is a hair follicle opener; and higher molecular weight aliphatic surfactants such as lauryl sulfate salts which change the surface state of the skin and drugs administered. Other agents include oleic and linoleic acids, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopheryl acetate, tocopheryl linoleate, propyl oleate, and isopropyl palmitate.

In certain embodiments of the invention a plasticizer or tackifying agent is incorporated into the formulation to improve the adhesive characteristics of the dermal composition. A tackifying agent is particularly useful in those embodiments in which the drug does not plasticize the polymer. Suitable tackifying agents are those known in the art including: (1) aliphatic hydrocarbons; (2) mixed aliphatic and aromatic hydrocarbons; (3) aromatic hydrocarbons; (4) substituted aromatic hydrocarbons; (5) hydrogenated esters; (6) polyterpenes; and (7) hydrogenated wood rosins. The tackifying agent employed is preferably compatible with the blend of polymers. In preferred embodiments, the tackifying agent is silicone fluid (*e.g.*, 360 Medical Fluid, available from Dow Corning Corporation, Midland, MI) or mineral oil. Silicone fluid is useful for blends comprising polysiloxane as a major component. In other embodiments, where polyacrylate, for example, is a major component, mineral oil is a preferred tackifying agent.

Some drugs, such as the vasodilator nitroglycerin, function as plasticizers in the composition because they are soluble to a certain degree in the polymers comprising the system. For drug molecules which are not readily soluble in the polymer system, a co-solvent for the drug and polymer can be added. Co-solvents, such as lecithin, retinol

derivatives, tocopherol, dipropylene glycol, triacetin, propylene glycol, saturated and unsaturated fatty acids, mineral oil, silicone fluid, alcohols, butyl benzyl phthalate, and the like are useful in the practice of the instant invention depending on the solubility of the drug in the multiple polymer adhesive system.

To summarize, the preferred and optimum compositions for the polyacrylate/polysiloxane embodiment are as follows:

TABLE II

Component	PERCENT BY WEIGHT Preferred Range	Optimum Range
Polysiloxane	97-4	97-14
Polyacrylate	2-95	2-85
Co-solvent(s)	0-30	0-20
Enhancer(s)	0-20	0-10
Drug(s)	0.3-50	1-30

The composition of this invention may further be provided with various thickeners, fillers and other additives known for use with dermal compositions. Where the composition tends to absorb water, for example, when lecithin is used as a co-solvent, hydrophilic fillers are especially useful. One type of hydrophilic filler which has been successfully employed is an aluminum silicate clay.

In a device aspect of the invention, the dermal composition can be used as an adhesive portion of any transdermal drug delivery device (*e.g.*, a reservoir device) or it can comprise an adhesive monolithic device. Of course, the principles of the invention would still apply to embodiments where the dermal composition is not a pressure-sensitive adhesive and comprises the drug reservoir.

Reference to FIG. 1 shows a schematic illustration of an adhesive monolithic device embodiment of the invention 10. The dermal composition comprises a monolithic body 11 of a defined geometric shape with a protective release liner 12 on one side of monolithic body 11 and a backing layer 13 on the other side. Removal of the release liner 12 exposes the pressure-sensitive multiple polymer adhesive which functions both as the drug carrier matrix and as the means of applying the system to the patient.

A device, or individual dosage unit, of the present invention can be produced in any manner known to those of skill in the art. After the dermal composition is formed, it may be brought into contact with the backing layer in any manner known to those of skill in the art. Such techniques include calender coating, hot melt coating, solution coating, *etc.* Of course, backing materials are well known in the art and can comprise plastic films of polyethylene, vinyl acetate resins, ethylene/vinyl acetate copolymers, polyvinyl chloride, polyurethane, and the like, metal foils, non-woven fabric, cloth and commercially available laminates. The backing material generally has a thickness in the range of 2 to 1000 micrometers and the dermal composition is generally disposed on backing material in a thickness ranging from about 12 to 250 micrometers thick.

Suitable release liners are also well known in the art and include the commercially available products of Dow Corning Corporation designated Bio-Release® liner and Syl-off® 7610 liner. For preferred embodiments in which a polysiloxane is part of the multiple polymeric adhesive system, the release liner must be compatible with the silicone adhesive. An

example of a suitable commercially available liner is 3M's 1022 Scotch Pak.

The configuration of the transdermal delivery system of the present invention can be in any shape or size as is necessary or desirable. Illustratively, a single dosage unit may have a surface area in the range of 1 to 200 cm^2. Preferred sizes are from 5 to 60 cm^2.

In a method aspect of the invention, a plurality of polymers having differing solubility parameters are blended (but not chemically reacted or cross-linked) to result in a dermal composition, or multiple polymer adhesive system with incorporated drug or bioactive agent, which controls delivery of an incorporated drug into and through the epidermis. The blending of polymers results in an adjustment of the saturation concentration of the drug in the polymeric system and therefore permits selective modulation of the transdermal drug delivery rate. The term "blending," of course, incorporates choosing the appropriate polymeric components, and the proportions thereof, to achieve the desired effect.

In a preferred embodiment of the invention, a dermal composition is prepared by mixing the polyacrylate, the polysiloxane, drug, co-solvent(s), and tackifying agent, if needed, in an appropriate volatile solvent(s), then casting the mixture and removing the solvent(s) by evaporation to form a film.

Suitable volatile solvents include, but are not limited to, alcohols such as isopropanol and ethanol; aromatics such as xylenes and toluene; aliphatics such as hexane, cyclohexane, and heptane; and alkanoic acid esters such as ethyl acetate and butyl acetate.

An exemplary general method of preparation is as follows:

1. Appropriate amounts of polysiloxane and polyacrylate, dissolved in a solvent(s), are combined and thoroughly mixed together in a vessel.

2. The drug is then added to the polymer mixture and agitation is carried out until the drug is uniformly mixed in.

3. Co-solvents and enhancers, if necessary, can then be added to the drug-polymer mixture, and thoroughly mixed.

4. The formulation is then transferred to a coating operation where it is coated onto a protective release liner at a controlled specified thickness.

5. The coated product is then passed through an oven in order to drive off all volatile processing solvents.

6. The dried product on the release liner is then joined to the backing material and wound into rolls for storage.

7. Appropriate size and shape dosage units are die-cut from the roll material and then pouched.

The order of steps, the amounts of ingredients, and the amount and time of agitation or mixing are process variables which will depend on the specific polymers, drug, co-solvents, and enhancers used in the formulation. These factors can be adjusted by those of skill in the art as required to provide a uniform product which has acceptable pressure-sensitive adhesive characteristics.

Examples

The following specific examples are included as illustrative of dermal compositions, and methods of making same, within the contemplation of the invention. These examples are in no way intended to be limiting of the scope of the invention.

The following commercially available adhesives were used in the blends comprising the multiple polymer adhesive system of the examples: "Duro-Tak 80-1194, 80-1196, and 80-1197" are trademarks of National Starch and Chemical Corporation, Bridgewater, New Jersey for acrylic adhesives (polyacrylates) in organic solutions.

"BIO-PSA X7-3027, X7-4919, X7-2685, and X7-3122" are trademarks of Dow Corning Corporation, Medical Products, Midland, Michigan for silicone adhesives (polysiloxanes) in organic solutions. BIO-PSA-3027 is particularly suitable for use in formulations containing amine-functional drugs, such as albuterol and pilocarpine, in the following examples.

"Vistanex LM-LS-LC" is a trademark of Exxon Chemical Company, Houston, Texas, for a polyisobutylene polymer with a Flory molecular weight of 42,600 to 46,100.

"Elvax 40-W" is a trademark of Du Pont Company, Wilmington, Delaware, for a polyethylene/vinyl acetate copolymer (40% vinyl acetate content).

The aforementioned polymeric adhesives are supplied, or prepared, as solutions wherein the percent solids by weight are as follows:

Ingredient	Percent Solids
BIO-PSA X7-3027	50
BIO-PSA X7-3122	65
BIO-PSA X7-4919	50
BIO-PSA X7-2685	50
Duro-Tak 80-1194	45
Duro-Tak 80-1196	45
Duro-Tak 80-1197	45
Elvax 40-W	30
Vistanex LM-MS-LC	30

"360 Medical Fluid" is a trademark of Dow Corning Corporation for a polydimethylsiloxane fluid. In certain embodiments of the invention, 360 Medical

Fluid is added as a tackifier to improve the adhesive characteristics of the end product.

EXAMPLE 1

A nitroglycerin-polymer mixture was prepared by combining 22.0 parts of nitroglycerin, 1.0 part of dipropylene glycol, 1.3 parts of lecithin, 0.8 parts of propylene glycol, 2.5 parts of 360 Medial Fluid (1000 cs), 1.0 part of bentonite, 63.6 parts of polyacrylate (Duro-Tak 80-1194), and 85.6 parts of polysiloxane (BIO-PSA X7-4919), and mixed well in an appropriate container. Nitroglycerin is available as a solution in solvents such as ethanol, toluene, and propylene glycol from ICI Americas Inc., Wilmington, Delaware. In this instance, the nitroglycerin was added as a solution in toluene mixed together with the polyacrylate. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, shown below.

COMPONENT	PERCENT BY WEIGHT
Polysiloxane (Dow Corning Silicone Adhesive X7-4919)	42.8
Polyacrylate (National Starch Acrylic Adhesive, Duro-Tak 80-1194)	28.6
Polydimethylsiloxane fluid (Dow Corning 360 Medical Fluid)	2.5
Lecithin	1.3
Propylene glycol	0.8
Dipropylene glycol	1.0
Bentonite	1.0
Nitroglycerin	22.0
	100.0

Nitroglycerin flux results through cadaver skin *in vitro* from the formulation of Example 1, Transderm-Nitro® (a trademark of Ciba-Geigy Corporation, Summit, NJ), and Nitro-Dur® (a trademark of Key Pharmaceuticals, Inc., Kenilworth, NJ) are summarized in FIG. 2. As shown in FIG. 2, nitroglycerin flux from the dermal composition of Example 1 (20.8 $\mu g/cm^2hr$) was approximately twice that from Transderm-Nitro® (9.5 $\mu g/cm^2hr$) and about 1.5 times that from Nitro-Dur® (13.4 $\mu g/cm^2hr$).

EXAMPLES 2 - 5

In the following examples (2-5), the method of Example 1 was used with the appropriate amounts of starting materials to yield compositions having the following ingredient concentrations set forth in tabular form in TABLE III. Example 2 is presented for comparative purposes and its formulation is not within the scope of the present invention. Example 3 and 5 are adhesive compositions comprising blends of polyacrylate and a second polymer selected to illustrate the principles of the invention. All other components, such as excipients or fillers, remain constant in composition and amount from Examples 2 to 5.

TABLE III

Ingredient (SP, $J^{1/2}/cm^{3/2}$)	Examples (%, w/w) 2	3	4	5
Polyacrylate (21)	73.2	33.1	33.1	33.1
Polyethylene vinyl acetate (21)	–	40.1	–	–
Polyisobutylene (17)	–	–	40.1	–
Polysiloxane (15)	–	–	–	40.1
Nitroglycerin (27)	20.8	20.8	20.8	20.8
Oleic acid	2.0	2.0	2.0	2.0
Propylene glycol	0.8	0.8	0.8	0.8
Lecithin	1.2	1.2	1.2	1.2
Dipropylene glycol	1.0	1.0	1.0	1.0
Bentonite	1.0	1.0	1.0	1.0

FIG. 3 graphically summarizes the *in vitro* nitroglycerin flux results through cadaver epidermis from the dermal compositions of Examples 2 to 5. As seen in FIG. 3, addition of either polyisobutylene (Example 4) or polysiloxane (Example 5) -- both with SPs lower than polyacrylate -- resulted in doubling of the nitroglycerin flux as compared to an all acrylate system (Example 2). However, addition of polyethylene vinyl acetate (Example 3) -- with an SP value similar to the polyacrylate -- resulted in little effect on nitroglycerin flux as compared to the system of Example 2. Thus, the formulation of Example 3 is not within the scope of the present invention.

EXAMPLE 6

A series of nitroglycerin-containing compositions (I-VI) were prepared in which the polyacrylate (X7-3122) to polysiloxane (Duro-Tak 80-1194) ratio was varied from 100.0 : 0.0 (all acrylic) to 0.0 : 100.0 (all siloxane) by weight. Nitroglycerin concentration was held at 20% for all compositions. The ingredient concentrations of these compositions are shown below in TABLE IV.

TABLE IV

	I	II	III	IV	V	VI
Polysiloxane	–	14.4	28.8	43.2	57.6	72.6
Silicone Fluid	–	1.6	3.2	4.8	6.4	8.0
Polyacrylate	80.0	64.0	48.0	32.8	16.0	–
Nitroglycerin	20.0	20.0	20.0	20.0	20.0	20.0

In vitro skin flux was determined for these compositions and the results are summarized in Table V and graphically depicted in FIG. 4.

TABLE V

	% of Polymer		(µg/cm 2/hr)	(hr)
Composition	Polyacrylate	Polysiloxane	GTN Flux	Tlag
I	100	0	1.6	0.0
II	81.6	18.4	3.2	1.5
III	62.5	37.5	4.2	2.0
IV	43.2	56.8	4.5	2.3
V	21.7	78.3	5.2	2.3
VI	0	100	4.9	2.4
Nitro-Dur®	–	–	3.0	2.5

As shown, nitroglycerin (GTN) flux increased as the concentration of polysiloxane in the multiple polymer adhesive matrix increased up to a maximum, at around 80% polysiloxane, after which no more increase in flux was seen. It appears that beyond a certain concentration of siloxane polymer, the nitroglycerin activity ceases to increase (unit activity is reached), and the flux no longer increases. The attainment of saturation concentration (unit activity) is further verified by the fact that Composition VI had nitroglycerin exudate; that is, the surface of the adhesive was "wet" with excess nitroglycerin. Of course, Composition VI, which is all polysiloxane, is not within the contemplation of the invention.

The composition of the blend of polymers is preferably chosen so that the flux rate of drug from the blend is at a maximum. Studies similar to those reported herein may be employed to assist in selecting the appropriate components of the blend and the weight ratios thereof. In alternative embodiments, it may be desirable to select a composition in which the flux rate will be retarded.

EXAMPLES 7 - 9

An estradiol-polymer mixture (Example 7) was prepared by combining 2.0 parts of 17β-estradiol, 2.0 parts of propylene glycol, 3.0 parts of lecithin, 5.0 parts of oleic acid, 5.0 parts of dipropylene glycol, 93.3 parts of polyacrylate (Duro-Tak 80-1196), and 63.1 parts of polysiloxane (BIO-PSA X7-3122), and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE VI.

Examples 8 and 9 were made in accordance with the method of Example 7. The compositions of Examples 8 and 9 have the same drug and additional components, such as the co-solvents, as Example 7, but are not within the scope of this invention inasmuch as the resulting adhesive matrices are single polymer systems. Examples 8 and 9 are given for comparative purposes only.

TABLE VI

Ingredient	Examples (%, w/w) 7	8	9
Polyacrylate	42.0	83.0	--
Polysiloxane	41.0	--	83.0
Estradiol	2.0	2.0	2.0
Oleic acid	5.0	5.0	5.0
Propylene glycol	2.0	2.0	2.0
Lecithin	3.0	3.0	3.0
Dipropylene glycol	5.0	5.0	5.0

Estradiol flux *in vitro* from the systems of Examples 7, 8, and 9 is shown in FIG. 5. As seen in FIG. 5, delivery from the system of this invention utilizing the multiple polymer adhesive (polyacrylate/polysiloxane) of Example 7 was substantially greater than delivery from the prior art systems comprising single polymer adhesives (Examples 8 and 9).

EXAMPLES 10 - 13

In the following examples (10-13), the method of Example 7 was used with the appropriate amounts of starting materials to yield compositions having the ingredient concentrations set forth in TABLE VII.

TABLE VII

Ingredient	Examples (%, w/w) 10	11	12	13
Polysiloxane	18.0	33.5	39.5	58.0
Polyacrylate	65.0	39.5	33.5	15.0
Estradiol	2.0	2.0	2.0	2.0
Oleic acid	5.0	5.0	5.0	5.0
Propylene glycol	2.0	2.0	2.0	2.0
Lecithin	3.0	3.0	3.0	3.0
Silicone fluid	5.0	15.0	15.0	15.0

FIG. 6 shows estradiol flux results for the compositions of Examples 10 - 13; average flux was calculated for each composition from 0 to 22 hours and

from 22 to 99 hours from the start of the study. As seen in FIG. 6, estradiol flux progressively increased with increased silicone polymer content during the first 22 hours of delivery, but was affected to a much lesser degree during the remainder of the study (22 to 99 hours). Thus, significant adjustment of the estradiol delivery rate during the initial phase of delivery was accomplished, with minor effects on the later delivery phase, by modulating the polysiloxane to polyacrylate polymer ratio. Fig 6 also illustrates that the delivery characteristics over time can be adjusted by the appropriate choice of polymers and respective weight ratios. For example, the formulation of Example 10 delivers drug at approximately the same rate over time whereas the formulation of Example 13 delivers more quickly in the early phase than the latter.

EXAMPLES 14 - 16

A norethindrone acetate-polymer mixture was prepared by combining 0.6 parts of norethindrone acetate, 1.0 parts of butylene glycol, and 40.9 parts of polyacrylate (Duro-Tak 80-1194), and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE VIII. The same method was employed to make Examples 15 and 16.

TABLE VIII

	Examples (% w/w)		
Ingredient	14	15	16
Polyacrylate	92.0	--	46.0
Polysiloxan	--	92.0	46.0
Norethindrone acetate	3.0	3.0	3.0
Butylene glycol	5.0	5.0	5.0

Norethindrone acetate flux *in vitro* from the systems of Examples 14, 15, and 16 is shown in FIG. 7. As seen in FIG. 7, norethindrone acetate delivery from the polyacrylate/polysiloxane systems of this invention (Example 16) was intermediate to delivery from the single polymer systems not of this invention (Example 14 and 15). Thus, blending the polyacrylate and polysiloxane results in modulation of the norethindrone acetate flux.

EXAMPLES 17 - 20

As estradiol/norethindrone acetate combination-polymer mixture was prepared by combining 0.6 parts of 17β estradiol, 0.6 parts of norethindrone acetate, 0.6 parts of butylene glycol, 0.6 parts of oleic acid, 1.5 parts of lecithin, 4.5 parts of silicone fluid (polydimethylsiloxane fluid, Dow Corning 360 Medical Fluid, 100 cs), and 43.2 parts of polysiloxane (BIO-PSA X7-4919), and mixing well in an appropriate container. The method of Example 17 was used with the appropriate amounts of starting materials to yield the compositions of Example 18, 19 and 20. The polyacrylate used in Examples 18-20 was National Starch Acrylic Adhesive, Duro-Tak 80-1197. The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE IX.

TABLE IX

Ingredient	Examples (% w/w) 17	18	19	20
Polysiloxan	72.0	68.0	60.0	47.0
Polyacrylate	--	5.0	15.0	30.0
Estradiol	2.0	2.0	2.0	2.0
Norethindrone acetate	2.0	2.0	2.0	2.0
Oleic acid	2.0	2.0	2.0	2.0
Butylene glycol	2.0	2.0	2.0	2.0
Lecithin	5.0	5.0	5.0	5.0
Silicone fluid	15.0	14.0	12.0	10.0

Flux results for the compositions of Examples 17-20 are shown in Fig. 8. As shown in Fig. 8, the flux of both estradiol (E2) and norethindrone acetate (NAc) varied as the polysiloxane to polyacrylate polymer ratio was adjusted; estradiol flux gradually increased and then decreased with a maximum at about 15% acrylate, and the norethindrone acetate flux continuously decreased with increasing acrylate content as would be expected from the data of Fig. 7. A further effect of varying the polysiloxane/polyacrylate polymer ratio is exhibited by a plot of estradiol flux relative to norethindrone acetate flux (estradiol flux divided by norethindrone acetate flux) as shown in Fig. 9. By adjusting the silicone to acrylate polymer ratio, it was possible to modulate the relative delivery of two drugs (estradiol and norethindrone acetate) from the systems of this invention.

EXAMPLES 21 - 23

A pilocarpine-polymer mixture was prepared by combining 5.0 parts of pilocarpine base, 1.2 parts of lecithin, 0.8 parts of propylene glycol, 2.0 parts of oleic acid, 2.5 parts of silicone fluid (polydimethylsiloxane, Dow Corning 360 Medical Fluid, 100 cs), and 77.0 parts of polysiloxane (Dow Corning Silicone Adhesive BIO-PSA X7-3027), and mixing well in an appropriate container. Example 22 incorporated pilocarpine into a polyacrylate comprising National Starch Acrylic Adhesive, Duro-Tak 80-1196. Example 23 employed a blend of polysiloxane and polyacrylate in accordance with the principles of the invention. The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE X.

TABLE X

Ingredient	Examples (% w/w) 21	22	23
Polyacrylate	--	82.0	41.0
Polysiloxane	77.0	--	41.0
Silicone Fluid	5.0	--	--
Pilocarpine	10.0	10.0	10.0
Oleic acid	4.0	4.0	4.0
Propylene glycol	1.6	1.6	1.6
Lecithin	2.4	2.4	2.4

Pilocarpine flux *in vitro* from the systems of Examples 21, 22, and 23 is shown in Fig. 10. As seen in Fig. 10, the delivery rate from the system of this invention utilizing the multiple polymer adhesive (polyacrylate/polysiloxane) of Example 23, was intermediate of the delivery rates from single polymer compositions (Examples 21 and 22) which are not of this invention. In this embodiment of the invention, the combination of polyacrylate and polysiloxane

polymers adjusted the delivery of rate of pilocarpine within the ranges established by single polymer compositions.

EXAMPLES 24 - 27

An albuterol-polymer mixture was prepared by combining 10.2 parts of albuterol base, 1.5 parts of lecithin, 1.0 part of propylene glycol, 4.1 parts of oleic acid, 2.6 parts of dipropylene glycol, 1.5 parts of butylene glycol, 1.5 parts of vitamin E acetate (tocoperyl acetate), 25.5 parts of polyacrylate (Duro-Tak 80-1196), 11.9 parts of polysiloxane A (BIO-PSA X7-3122), 20.1 parts of polysiloxane B (BIO-PSA X7-3027), and 20.1 parts of isopropyl alcohol, and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in Table XI.

The method of Example 24 was used with the appropriate amounts of starting materials to yield the compositions of Examples 25, 26, and 27.

TABLE XI

	Examples (% w/w)			
Ingredient	24	25	26	27
Polysiloxane A	14.0	13.8	14.0	14.0
Polysiloxane B	19.6	19.2	28.0	19.6
Polyacrylate	22.4	22.0	20.0	22.4
Albuterol	20.0	20.0	20.0	20.0
Oleic acid	8.0	8.0	8.0	8.0
Propylene glycol	2.0	2.0	2.0	2.0
Dipropylene glycol	5.0	5.0	5.0	5.0
Butylene glycol	3.0	3.0	--	3.0
Vitamin E acetate	3.0	3.0	--	--
Vitamin E	--	1.0	--	--
Vitamin E linoleate	--	--	--	3.0
Lecithin	3.0	3.0	3.0	3.0

Albuterol flux results through human cadaver skin *in vitro* from the formulations of Examples 24, 25, 26, and 27, are summarized in Fig. 11; nitroglycerin flux from Nitro-Dur® through the same skin specimen is shown as a control. Flux values for the albuterol compositions of Example 24 to 27 ranged from about 17 $\mu g/cm^2/hr$ to about 22 $\mu g/cm^2/hr$. The nitroglycerin flux value of about 28 $\mu g/cm^2/hr$ was slightly higher than the literature delivery rate for this product (20 $\mu g/cm^2/hr$, based on Nitro-Dur® product label of 0.1 mg/hr from a 5 cm^2 system). In order to adjust for the apparent higher permeability of the skin specimen, albuterol flux results can be multiplied by an adjustment factor of 0.714 (20/28); this would result in flux values of about 12 $\mu g/cm^2/hr$ to about 16 $\mu g/cm^2/hr$.

Therapeutic albuterol plasma concentrations are in the range of about 4 to 8 ng/mL, and are produced by delivery rates of about 115 to 230 $\mu g/hr$. The flux rates (12 to 16 $\mu g/cm^2/hr$) obtained from the compositions of this invention therefore would produce the necessary albuterol plasma levels (4 to 8 ng/mL) for the treatment of asthma from system sizes of about 10 to 20 cm^2.

EXAMPLES 28 - 29

Estradiol-polymer mixtures were prepared in accordance with the method of Example 7. Example 28 is illustrative of a multiple polymer adhesive system where polyacrylate is blended with polyisobutylene (Vistanex LM-LS-LC). The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE XII.

TABLE XII

Ingredient	Examples (%, w/w) 28	29
Polyacrylate	45.0	45.0
Polyisobutylene	45.0	—
Polysiloxane	—	45.0
Estradiol	2.0	2.0
Oleic acid	5.0	5.0
Lecithin	3.0	3.0

Estradiol flux *in vitro* from the systems of Examples 28 and 29 are shown in FIG. 12. As seen in FIG. 12, delivery from the multiple polymer adhesive system of Example 28 is comparable to delivery from Example 29.

EXAMPLE 30

In addition to flux measurements, the apparent diffusion coefficient, D, was calculated from release data for nitroglycerin from matrices of Compositions I to VI (Example 6) into an infinite sink. The method of D.R. Paul, <u>Controlled Release Polymeric Formulations, ACS Symposium Series No. 33</u>, Chapter 1 (1976) was used wherein the initial concentration of nitroglycerin in the matrix, C_0, was determined (assuming a density of 1.0) and the relationship of the amount released, M_t, by a matrix of area, A, and the diffusion coefficient is defined by:

$$M_t/A = 2C_o (Dt/\pi)^{1/2}$$

Plotting, M_t/A against $t^{1/2}$, results in a graph having a slope, m, defined by:

$$m = 2C_o (D/\pi)^{1/2}$$

The value of m can be ascertained by linear regression to get the slope of the best fit line. The diffusion coefficient is calculated as:

$$D = \pi(m/2C_o)^2$$

The results of these calculations for Compositions I to VI are shown below in Table XII.

TABLE XIII

Composition	Cs (mg/cm³)	Jm (mg/cm²h$^{1/2}$)	D (cm²/sec)	D(x10⁹)
I	241.0	0.8728	2.861×10^{-9}	2.86
II	233.3	0.9483	3.605×10^{-8}	36.05
III	231.3	1.0834	4.786×10^{-8}	47.86
IV	219.7	1.2502	7.065×10^{-8}	70.65
V	217.0	1.5920	1.174×10^{-7}	117.4
VI	215.0	2.4551	2.845×10^{-7}	284.5
Nitro-Dur	380.0	1.4680	3.256×10^{-8}	32.56

FIGS. 13 and 14 show the relationship of flux rate (J) plotted against apparent diffusion coefficient (D) and net solubility parameter (SP), respectively, for Compositions I-VI. The net solubility parameter, SP_{net}, was calculated using a weighted average of the solubility parameters of the individual polymers comprising the matrix:

$$SP_{net} = \emptyset_{ps}SP_{ps} + \emptyset_{pa}SP_{pa},$$

where $\emptyset_{ps}$ is the weight percentage of polysiloxane and SP_{ps} is the solubility parameter of polysiloxane. The subscript "pa" refers to the polyacrylate. FIG. 15 is a plot of diffusion coefficient versus net solubility parameter.

Although the invention has been described in terms of specific embodiments and applications, persons skilled in the art can, in light of this teaching, generate additional embodiments without exceeding the scope or departing from the spirit of the claimed invention. Accordingly, it is to be understood that the drawing and description in this disclosure are proffered to facilitate comprehension of the invention, and should not be construed to limit the scope thereof.

CLAIMS

1. An improved pressure-sensitive adhesive composition of the type suitable for controlled release of a bioactive agent from a pressure-sensitive adhesive matrix, the composition comprising:

a blend of a first polymeric adhesive having a first solubility parameter and a second polymeric adhesive having a second solubility parameter, the first and second solubility parameters being different from one another by an increment of at least 2 $(J/cm^3)^{1/2}$ and resulting in a characteristic net solubility parameter of the blend which can selectably adjust the saturation concentration of a bioactive agent contained in the pressure-sensitive adhesive composition and thereby modulate the release of the bioactive agent.

2. A transdermal drug delivery system comprising

(1) a blend of:

(a) a first polymeric material having a first solubility parameter, and

(b) a second polymeric material having a second solubility parameter, said first and second solubility parameters being different from one another and resulting in a preselected net solubility parameter of the blend; and

(2) a drug, wherein the net solubility parameter of the blend is preselected to determine the solubility of the drug in the blend.

3. The transdermal drug delivery system of claim 2 wherein the blend is a pressure-sensitive adhesive.

4. The tr··sdermal drug delivery system of claim 3 further com‚ -sing a backing material superimposed on

one surface of the pressure sensitive adhesive, said backing material being substantially impermeable to the drug contained therein.

5. The transdermal drug delivery system of claim 3 further comprising a release liner superimposed on a surface of the pressure sensitive adhesive opposite said backing material.

6. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is a steroid.

7. The transdermal drug delivery system of claim 6 wherein the steroid is an estrogen selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

8. The transdermal drug delivery system of claim 6 wherein the steroid is a progestational agent.

9. The transdermal drug delivery system of claim [7] 8 wherein the progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

10. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is a β_2-adrenergic agonist.

11. The transdermal drug delivery system of claim [7] 10 wherein the β_2-adrenergic agonist is selected from the group consisting of metaproterenol,

terbutaline, albuterol, carbuterol, rimiterol, salmefamol, fenoterol, soterenol, tratoquinol, and quinterenol.

12. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is a cardioactive agent.

13. The transdermal drug delivery system of claim 12 wherein said cardioactive agent is selected from the group consisting of nitroglycerin, isosorbide dinitrate, isosorbide mononitrates, quinidine sulfate, procainamide, benzydroflumethiazide, bendroflumethiazide, chlorothiazide, nifedipine, nicardipine, verapamil, diltiazem, timolol, propranolol, captopril, clonidine and prazosin.

14. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is a cholinergic agonist.

15. The transdermal drug delivery system of claim 14 wherein the cholinergic agonist is selected from the group consisting of choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.

16. The transdermal drug delivery system of [claim 2] any one of claims 2 to 15, wherein the drug is intimately mixed with the blend.

17. The transdermal drug delivery system of [claim 2] any one of claims 2 to 16, wherein said system is a reservoir device having an adhesive portion comprised of said blend.

18. The transdermal drug delivery system of [claim 2] any one of claims 2 to 17, wherein said first polymeric material is a polyacrylate.

19. The transdermal drug delivery system of claim 18 wherein the second polymeric material is a polysiloxane.

20. The transdermal drug delivery system of claim 19 wherein the polyacrylate is present in an amount ranging from about 2% to about 96% by weight of the blend and the polysiloxane is present in an amount ranging from about 98% to about 4% by weight of the blend.

21. The transdermal drug delivery system of claim 7 wherein the estrogen is 17β-estradiol and the 17β-estradiol is present in the system in an amount of from about 1% to about 5% by weight.

22. The transdermal drug delivery system of claim 9 wherein the progestational agent is norethindrone acetate and the norethindrone acetate is present in the system in an amount of from about 1% to about 5% by weight.

23. The transdermal drug delivery system of claim 11 wherein the β_2-adrenergic agonist is albuterol and the albuterol is present in the system in an amount of less than about 30% by weight.

24. The transdermal drug delivery system of claim 13 wherein the cardioactive agent is nitroglycerin and the nitroglycerin is present in the system in an amount of less than about 25% by weight.

25. The transdermal drug delivery system of claim 15 wherein the cholinergic agonist is pilocarpine and the pilocarpine is present in the drug-containing polymeric diffusion matrix in an amount of less than about 30% by weight.

26. The transdermal drug delivery system of [claim 2] <u>any one of claims 2 to 5,</u> wherein the drug is a tranquilizer.

27. The transdermal drug delivery system of claim 26 wherein the tranquilizer is selected from the group consisting of alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam,

clonazepam, flurazepam, triazolam, lorazepam and diazepam.

28. The transdermal drug delivery system of claim 27 wherein the tranquilizer is alprazolam.

29. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is an antipsychotic.

30. The transdermal drug delivery system of claim 29 wherein the antipsychotic is selected from the group consisting of thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine and molindone.

31. The transdermal drug delivery system of claim 30 wherein the antipsychotic is haloperidol.

32. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is an anesthetic.

33. The transdermal drug delivery system of claim 32 wherein the anesthetic is selected from the group consisting of lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine and benzocaine.

34. The transdermal drug delivery system of claim 33 wherein the anesthetic is lidocaine.

35. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug is an analgesic.

36. The transdermal drug delivery system of claim 35 wherein the analgesic is selected from the group consisting of fentanyl, buprenorphine and codeine.

37. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, wherein the drug has an action on the central nervous system.

38. The transdermal drug delivery system of claim 37 wherein the drug is nicotine.

39. The transdermal drug delivery system of [claim 2] any one of claims 2 to 5, comprising a mixture of at least two drugs.

40. The transdermal drug delivery system of claim 39 comprising a mixture of a progestational agent and an estrogen.

41. The transdermal drug delivery system of claim 40 wherein said progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

42. The transdermal drug delevery system of claim 41 wherein said progestational agent is norethindrone acetate.

43. The transdermal drug delivery system of claim [46] 40 wherein said estrogen is selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

44. The transdermal drug delivery system of claim 43 wherein said estrogen is 17β-estradiol.

45. The transdermal drug delivery system of [claim 2] any one of claims 2 to 44, wherein the first and second solubility parameters are different from one another by an increment of at least about 2 $(J/cm^3)^{1/2}$.

46. The transdermal drug delivery system of claim 45 wherein the first and second solubility parameters are different from one another by an increment of at least about 4 $(J/cm^3)^{1/2}$.

47. The transdermal drug delivery system of [claim 2] <u>any one of claims 2 to 46,</u> wherein said system achieves an increased permeation rate of the drug through the dermis of a subject relative to the permeation rate achieved by a system comprising said first polymeric material as the sole polymeric material.

48. The transdermal drug delivery system of [claim 2] <u>any one of claims 2 to 46,</u> wherein said system achieves a decreased permeation rate of the drug through the dermis of a subject relative to the permeation rate achieved by a system comprising said first polymeric material as the sole polymeric material.

49. The transdermal drug delivery system of [claim 2] <u>any one of claims 2 to 48,</u> further comprising an additive selected from the group consisting of an enhancer, a filler, a co-solvent and an excipient.

[50.]<u>51</u> A transdermal drug delivery system comprising:

(a) a multiple polymer adhesive system consisting essentially of a blend of about 2% to about 96% by weight of an acrylic-based polymer and about 98% to about 4% by weight of a silicone-based polymer, the multiple polymer adhesive system being in an amount of about 99% to about 50% by weight of the system;

(b) a drug in the amount of about 0.3% to about 50% by weight of the system;

(c) an effective amount of a co-solvent for the drug, said amount being up to about 30% by weight of the system; and

an effective amount of an enhancer, said amount being up to about 20% by weight of the system.

[51.]52. The transdermal drug delivery system of claim 50 further comprising fillers and excipients in an amount of about 1% to about 15% by weight of the dermal adhesive composition.

[52.]50. The transdermal drug delivery system of claim 2 comprising at least two drugs.

53. A method of making a transdermal drug delivery system of the type having a drug-containing pressure-sensitive adhesive, the method comprising the steps of:

(1) producing a mixture of

(a) a blend of a first polymeric material having a first solubility parameter, and a second polymeric material having a second solubility parameter, said first and second solubility parameters being different from one another and resulting in a preselected net solubility parameter of the blend, and

(b) a drug; and

(2) forming the mixture into a pressure-sensitive adhesive matrix.

54. The method of claim 53 further comprising the step of applying a backing material to one side of the pressure-sensitive adhesive matrix, said backing material being substantially impermeable to the drug contained therein.

55. The method of claim 54 further comprising the step of applying a release liner to a surface of the pressure-sensitive adhesive matrix opposite said backing material.

56. The method of [claim 53] any one of claims 53 to 55, wherein an additive selected from the group consisting of an enhancer, a filler, a co-solvent and an excipient is combined with said mixture prior to forming the mixture into the pressure-sensitive adhesive matrix.

57. The method of [claim 53] any one of claims 53 to 56, wherein the drug is intimately mixed with the blend.

58. The method of [claim 53] any one of claims 53 to 57, wherein said system is a reservoir device having an adhesive portion comprised of said blend.

59. The method of [claim 53] any one of claims 53 to 58, wherein said first polymeric material is a polyacrylate.

60. The method of claim 59 wherein the second polymeric material is a polysiloxane.

61. The method of claim 60 wherein the ratio of polyacrylate to polysiloxane is from about 2:98 to about 96:4 by weight of the pressure-sensitive adhesive matrix.

62. The method of claim 61 wherein the ratio of polyacrylate to polysiloxane is from about 2:98 to about 90:10 by weight of the pressure-sensitive adhesive matrix.

63. The method of claim 62 wherein the ratio of polyacrylate to polysiloxane is from about 2:98 to about 86:14 by weight of the pressure-sensitive adhesive matrix.

64. The method of [claim 53] any one of claims 53 to 63, wherein the drug is present in an amount ranging from about 0.3% to about 50% by weight of the pressure-sensitive adhesive matrix.

65. The method of [claim 53] any one of claims 53 to 64, wherein the drug is a steroid.

66. The method of claim 65 wherein the steroid is an estrogen selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

67. The method of claim 66 wherein the estrogen is 17β-estradiol and the 17β-estradiol is present in the pressure-sensitive adhesive matrix in an amount of from about 1% to about 5% by weight.

68. The method of claim 65 wherein the steroid is a progestational agent.

69. The method of claim 68 wherein the progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone,, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

70. The method of claim 69 wherein the progestational agent is norethindrone acetate and the norethindrone acetate is present in the pressure-sensitive adhesive matrix in an amount of from about 1% to about 5% by weight.

71. The method of [claim 53] <u>any one of claims 53 to 64,</u> wherein the drug is a β_2-adrenergic agonist.

72. The method of claim 53 wherein the β_2-adrenergic agonist is selected from the group consisting of metaproterenol, terbutaline, albuterol, carbuterol, rimiterol, salmefamol, fenoterol, soterenol, tratoquinol, and quinterenol.

73. The method of claim 72 wherein the β_2-adrenergic agonist is albuterol and the albuterol is present in the pressure-sensitive adhesive matrix in an amount of less than about 30% by weight.

74. The method of [claim 53] <u>any one of claims 53 to 64,</u> wherein the drug is a cardioactive agent.

75. The method of claim 74 wherein said cardioactive agent is selected from the group consisting of nitroglycerin, isosorbide dinitrate, isosorbide mononitrates, quinidine sulfate, procainamide, benzydroflumethiazide, bendroflumethiazide, chlorothiazide, nifedipine, nicardipine, verapamil, diltiazem, timolol, propranolol, captopril, clonidine and prazosin.

76. The method of claim 75 wherein the cardioactive agent is nitroglycerin and the nitroglycerin is present in the pressure-sensitive adhesive matrix in an amount of less than about 25% by weight.

77. The method of [claim 53] <u>any one of claims 53 to 64,</u> wherein the drug is a cholinergic agonist.

78. The method of claim 77 wherein the cholinergic agonist is selected from the group consisting of choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.

79. The method of claim 78 wherein the cholinergic agonist is pilocarpine and the pilocarpine is present in the pressure-sensitive adhesive matrix in an amount of less than about 30% by weight.

80. The method of claim 53 wherein the drug is a tranquilizer.

81. The method of claim 80 wherein the tranquilizer is selected from the group consisting of alprazolam, chlordiazepoxide, clorazeptate, halazepam,

oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

82. The method of claim 81 wherein the tranquilizer is alprazolam.

83. The method of [claim 53] any one of claims 53 to 64, wherein the drug is an antipsychotic.

84. The method of claim 83 wherein the antipsychotic is selected from the group consisting of thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine and molindone.

85. The method of claim 84 wherein the antipsychotic is haloperidol.

86. The method of [claim 53] any one of claims 53 to 64, wherein the drug is an anesthetic.

87. The method of claim 86 wherein the anesthetic is selected from the group consisting of lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine and benzocaine.

88. The method of claim 87 wherein the anesthetic is lidocaine.

89. The method of [claim 53] any one of claims 53 to 64, wherein the drug is an analgesic.

90. The method of claim 89 wherein the analgesic is selected from the group consisting of fentanyl, buprenorphine and codeine.

91. The method of [claim 53] any one of claims 53 to 64, wherein the drug has an action on the central nervous system.

92. The method of claim 91 wherein the drug is nicotine.

93. The method of [claim 53] any one of claims 53 to 64, wherein a mixture of at least two drugs is combined with said blend of polymeric materials.

94. The method of claim 93 wherein said mixture of drugs comprises a progestational agent and an estrogen.

95. The method of claim 94 wherein said progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

96. The method of claim 95 wherein said progestational agent is norethindrone acetate.

97. The method of claim 94 wherein said estrogen is selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

98. The method of claim 97 wherein said estrogen is 17β-estradiol.

99. The method of [claim 53] any one of claims 53 to 98, wherein the first and second solubility parameters are different from one another by an increment of at least about 2 $(J/cm^3)^{1/2}$.

100. The method of claim 99 wherein the first and second solubility parameters are different from one another by an increment of at least about 4 $(J/cm^3)^{1/2}$.

101. A method of adjusting the solubility of a drug in a transdermal drug delivery system which comprises the step of blending a plurality of polymers

having differing solubility parameters, so as to achieve a predetermined net solubility parameter, wherein at least two of said plurality of polymers have solubility parameters differing by at least about 2 $(J/cm^3)^{1/2}$.

102. The method of claim 101 wherein the first and second solubility parameters are different from one another by an increment of at least about 4 $(J/cm^3)^{1/2}$.

103. A method of modulating the delivery rate of a drug from a transdermal drug delivery system of the type having a pressure-sensitive adhesive matrix, which method comprises the steps of:

(a) selecting at least two immiscible polymeric materials as components of a multiple polymer adhesive system such that the system has a preselected net solubility parameter which results in a modified solubility of a drug in the system; and

(b) combining said at least two polymeric materials with a drug to form a pressure-sensitive adhesive matrix, wherein the matrix achieves a drug delivery rate which is determined by said preselected net solubility parameter and which differs from the delivery rate achieved by a pressure-sensitive adhesive matrix comprising a single one of said at least two polymeric materials as the sole polymeric material.

104. The method of claim 103 wherein the drug is intimately mixed with the at least two polymeric materials in the pressure-sensitive adhesive matrix.

105. The method of claim 104 wherein said polymeric materials and said drug are combined to form a reservoir device having an adhesive portion comprised of a blend of said polymeric materials.

106. The method of [claim 103] any one of claims 103 to 105, wherein said step of selecting comprises the step of measuring the flux rate from various weight ratios of the selected at least two immiscible polymers and choosing the ratio producing a preselected flux rate.

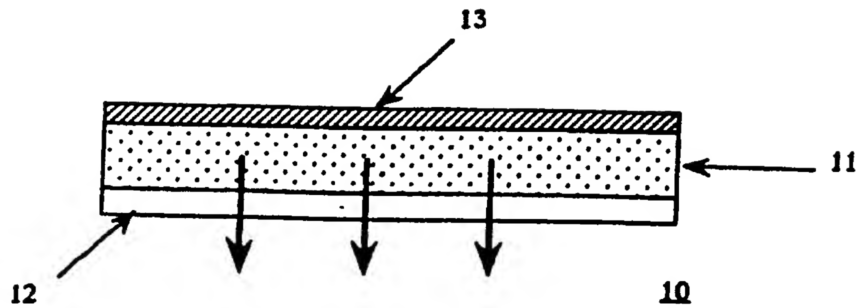


FIG. 1

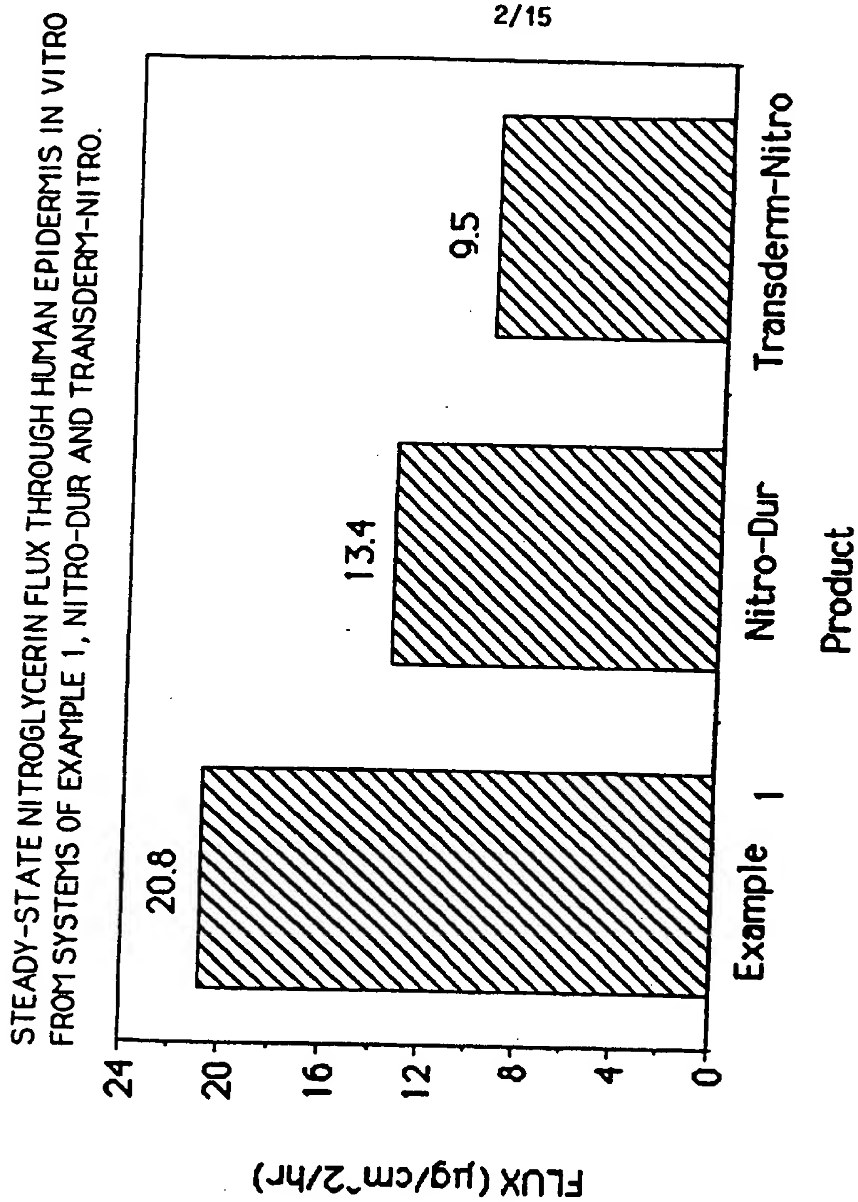

STEADY-STATE NITROGLYCERIN FLUX THROUGH HUMAN EPIDERMIS IN VITRO
FROM SYSTEMS OF EXAMPLE 1, NITRO-DUR AND TRANSDERM-NITRO.
FLUX (µg/cm^2/hr)
24
20
16
12
8
4
0
20.8
13.4
9.5
Example 1
Nitro-Dur
Transderm-Nitro
Product

FIG. 2

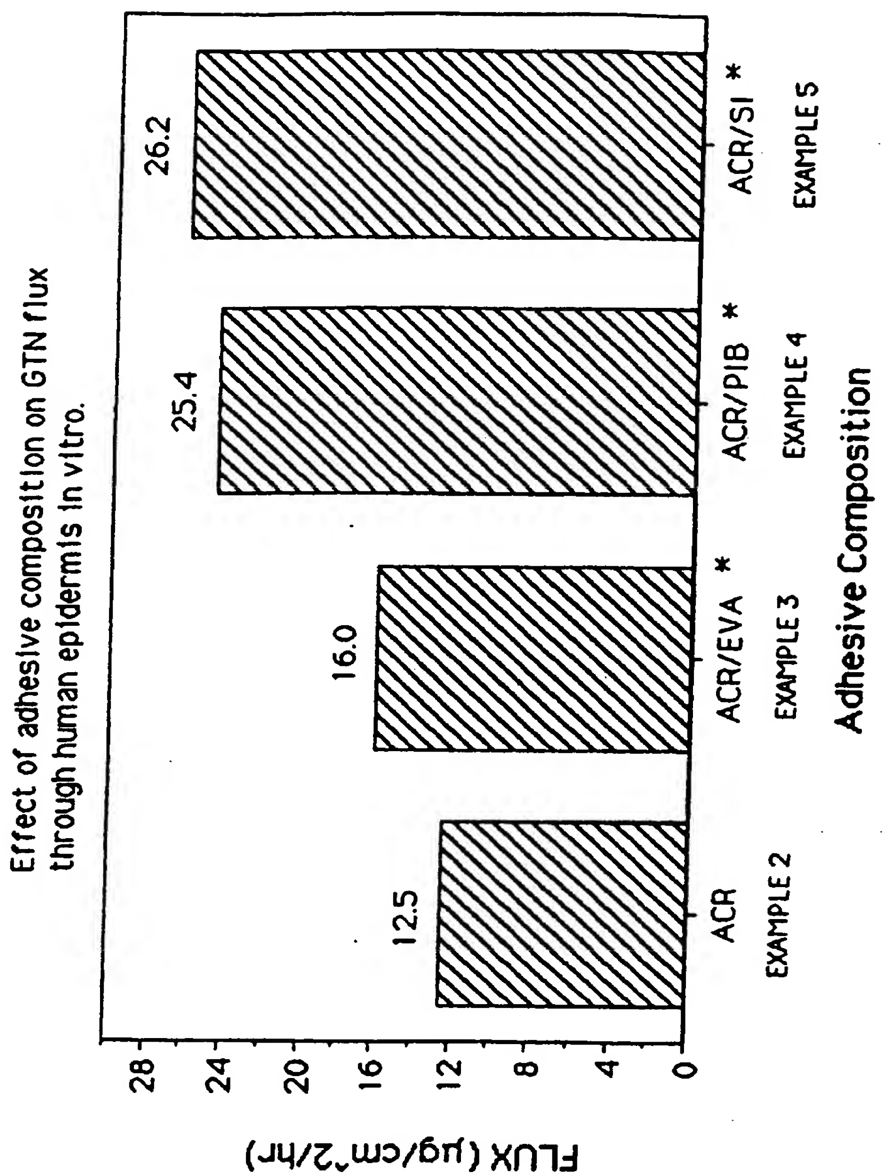


FIG. 3

*ACR/POLYMER ratios of 45/55, w/w.

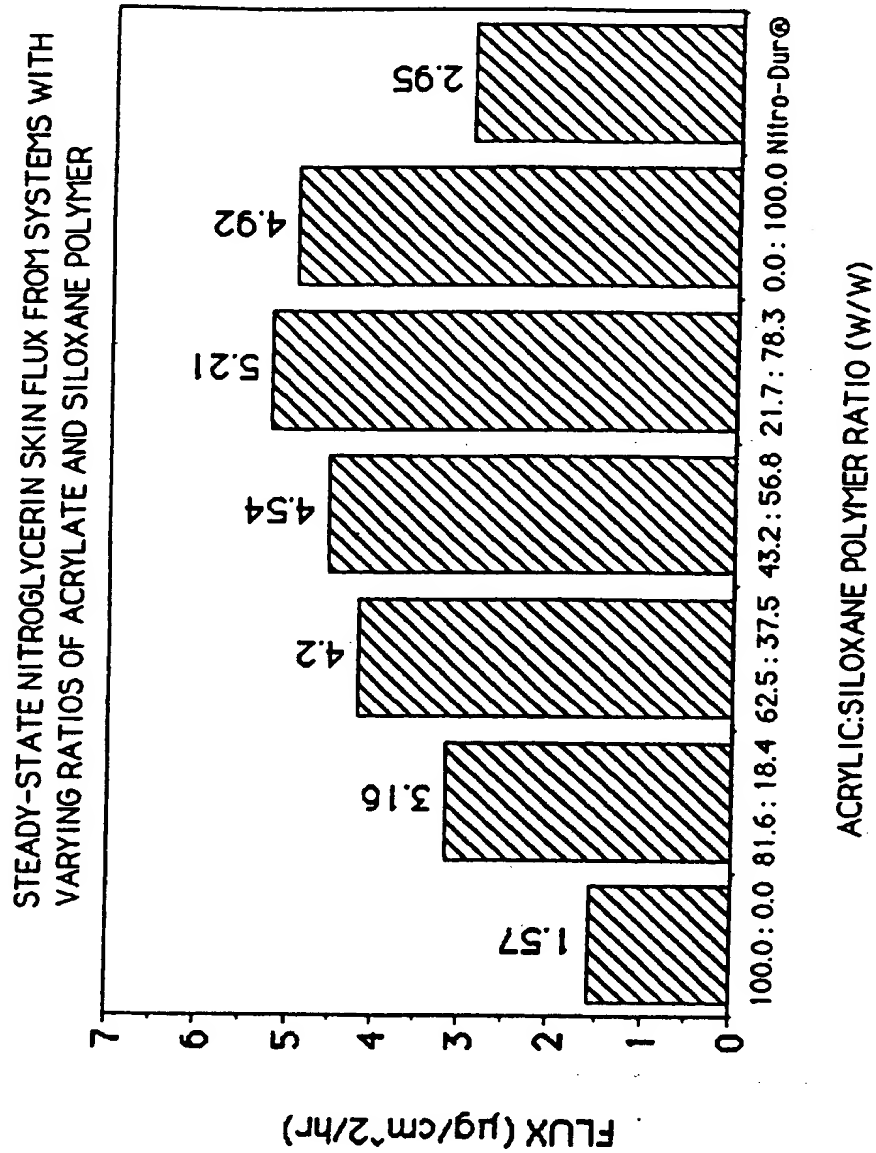
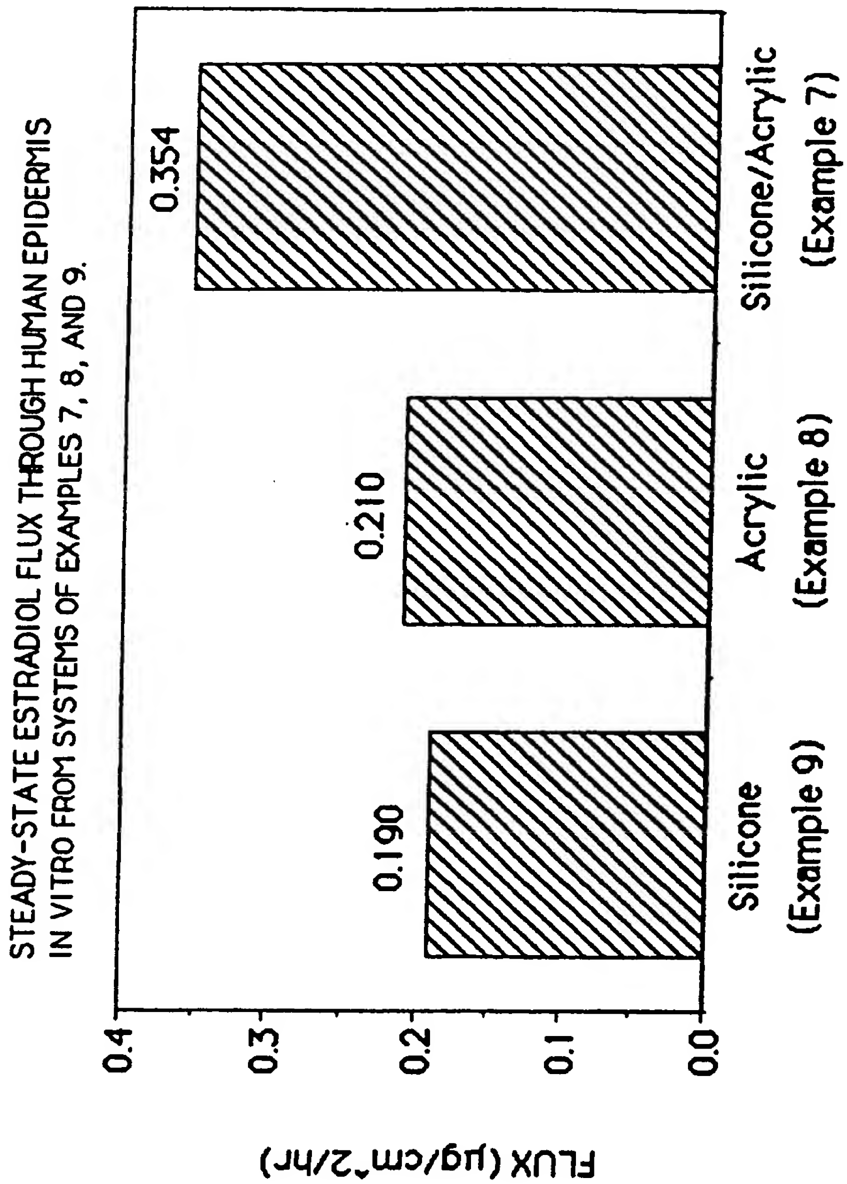

STEADY-STATE NITROGLYCERIN SKIN FLUX FROM SYSTEMS WITH VARYING RATIOS OF ACRYLATE AND SILOXANE POLYMER
FLUX (µg/cm^2/hr)
0
1
2
3
4
5
6
7
1.57
3.16
4.2
4.54
5.21
4.92
2.95
100.0 : 0.0
81.6 : 18.4
62.5 : 37.5
43.2 : 56.8
21.7 : 78.3
0.0 : 100.0
Nitro-Dur®
ACRYLIC:SILOXANE POLYMER RATIO (W/W)

FIG. 4



STEADY-STATE ESTRADIOL FLUX THROUGH HUMAN EPIDERMIS
IN VITRO FROM SYSTEMS OF EXAMPLES 7, 8, AND 9.
FLUX (µg/cm^2/hr)
0.0
0.1
0.2
0.3
0.4
0.190
0.210
0.354
Silicone
(Example 9)
Acrylic
(Example 8)
Silicone/Acrylic
(Example 7)

FIG. 5

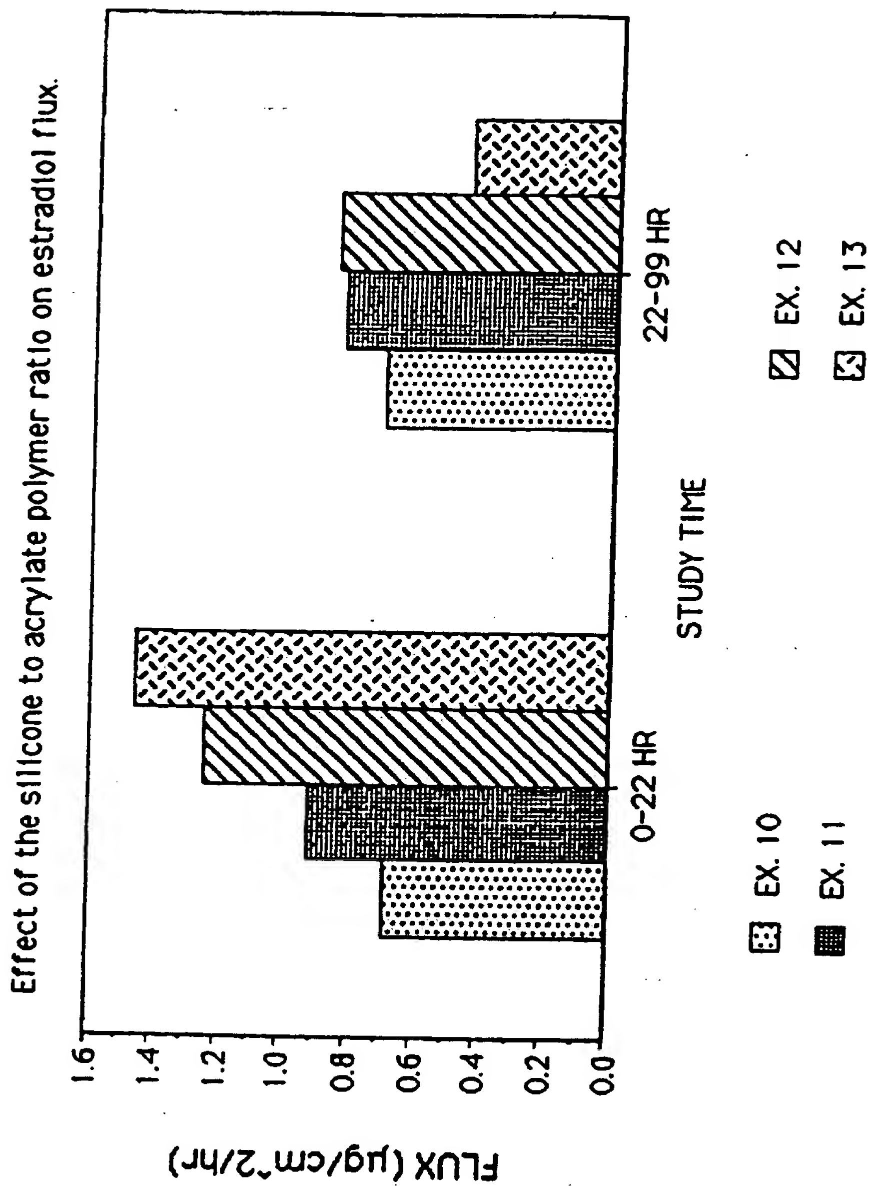

Effect of the silicone to acrylate polymer ratio on estradiol flux.
FLUX (µg/cm^2/hr)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0-22 HR
22-99 HR
STUDY TIME
EX. 10
EX. 11
EX. 12
EX. 13

FIG. 6

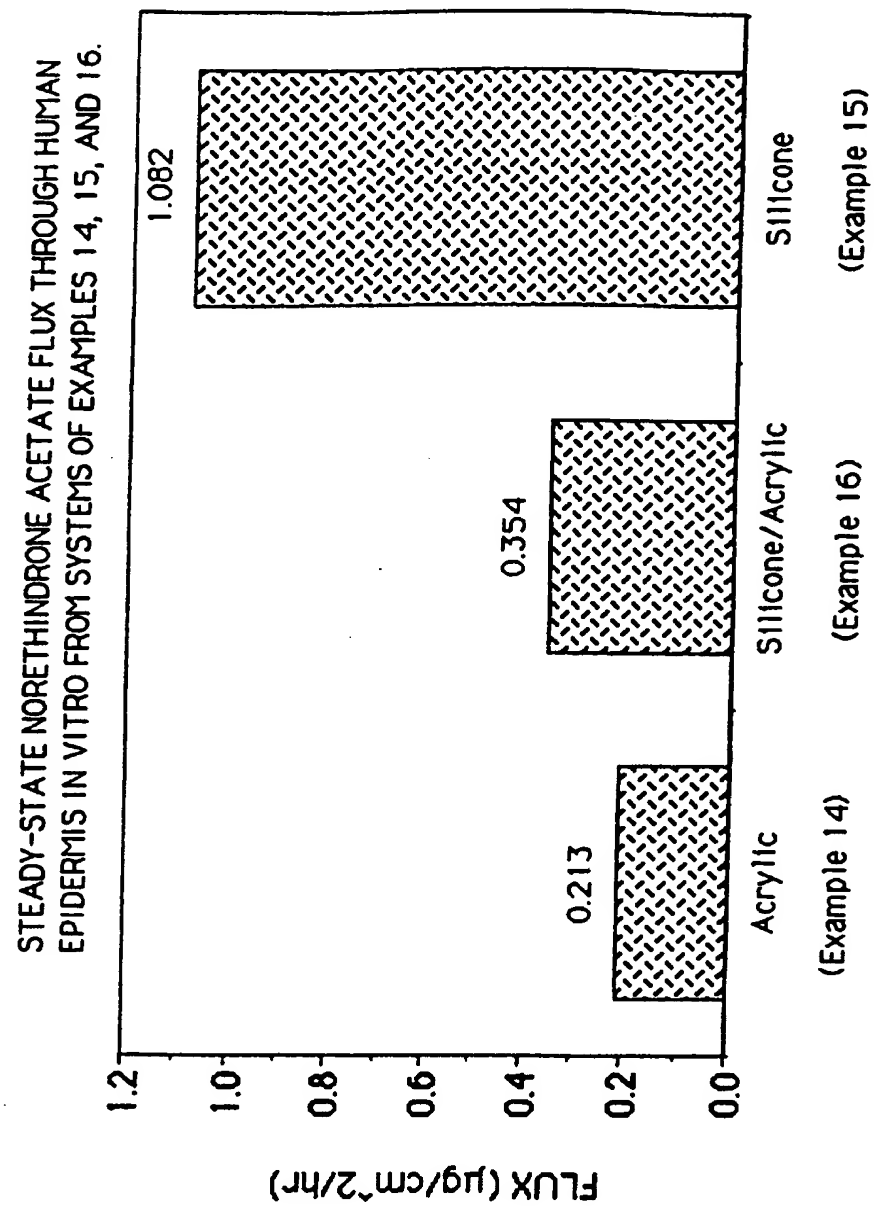

STEADY-STATE NORETHINDRONE ACETATE FLUX THROUGH HUMAN EPIDERMIS IN VITRO FROM SYSTEMS OF EXAMPLES 14, 15, AND 16.
FLUX (μg/cm^2/hr)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.213
0.354
1.082
Acrylic
(Example 14)
Silicone/Acrylic
(Example 16)
Silicone
(Example 15)

FIG. 7

Effect of the polysiloxane/polyacrylate polymer ratio on estradiol (E2) and norethindrone acetate (NAC) flux through human epidermis from E2/NAC combination systems of Examples 17-20.

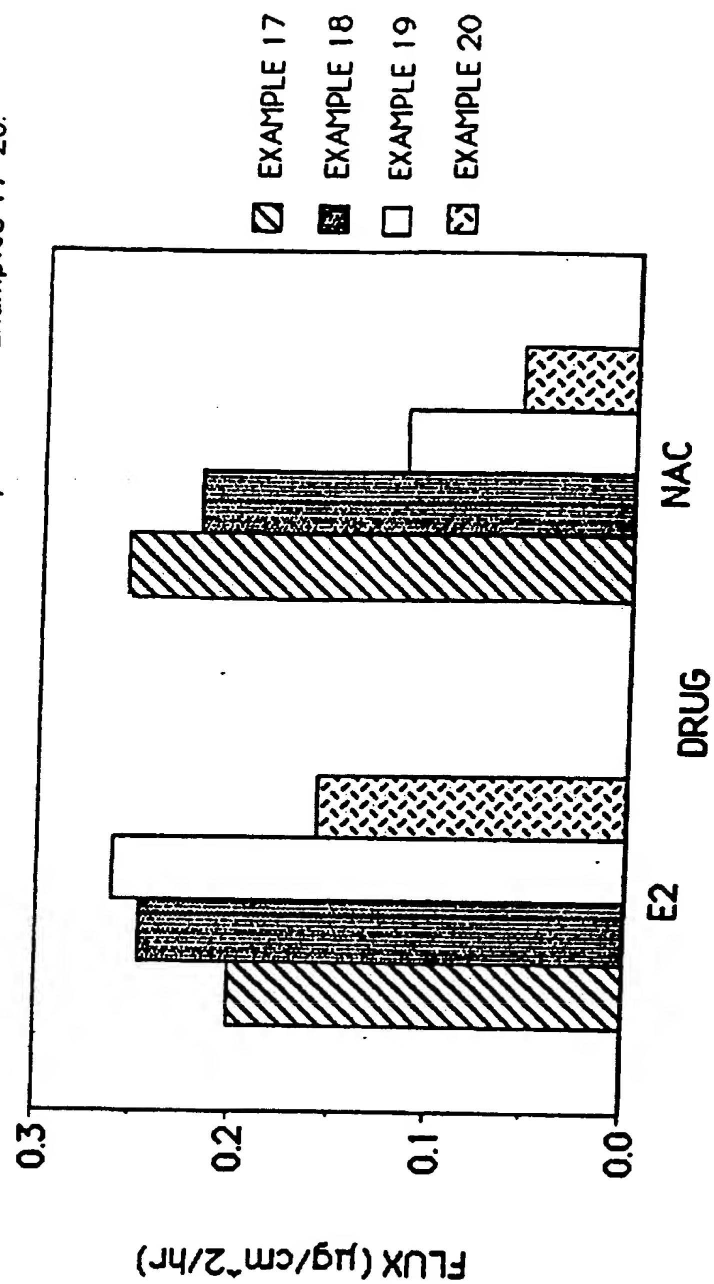


FIG. 8

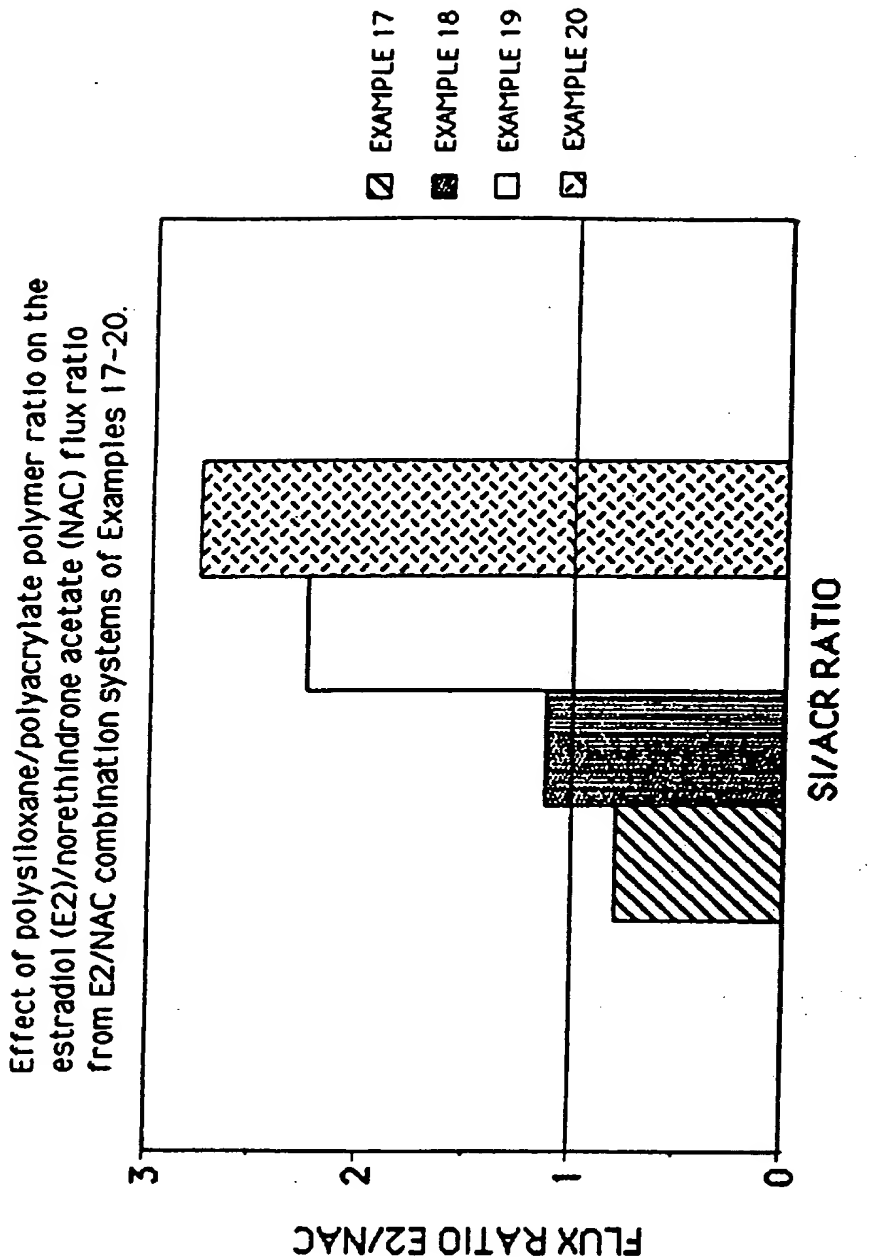

Effect of polysiloxane/polyacrylate polymer ratio on the estradiol (E2)/norethindrone acetate (NAC) flux ratio from E2/NAC combination systems of Examples 17-20.
EXAMPLE 17
EXAMPLE 18
EXAMPLE 19
EXAMPLE 20
FLUX RATIO E2/NAC
0
1
2
3
SI/ACR RATIO

FIG. 9

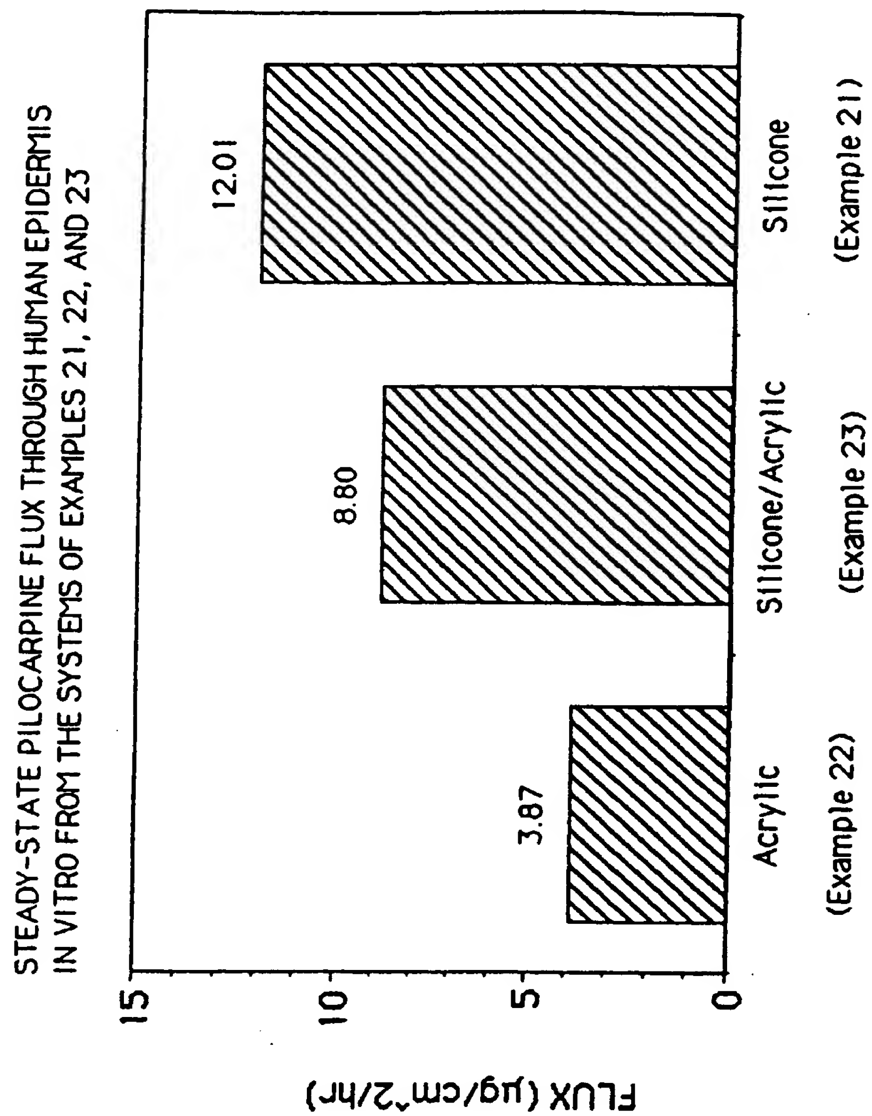

STEADY-STATE PILOCARPINE FLUX THROUGH HUMAN EPIDERMIS
IN VITRO FROM THE SYSTEMS OF EXAMPLES 21, 22, AND 23
FLUX (µg/cm^2/hr)
0
5
10
15
3.87
8.80
12.01
Acrylic
(Example 22)
Silicone/Acrylic
(Example 23)
Silicone
(Example 21)

FIG. 10

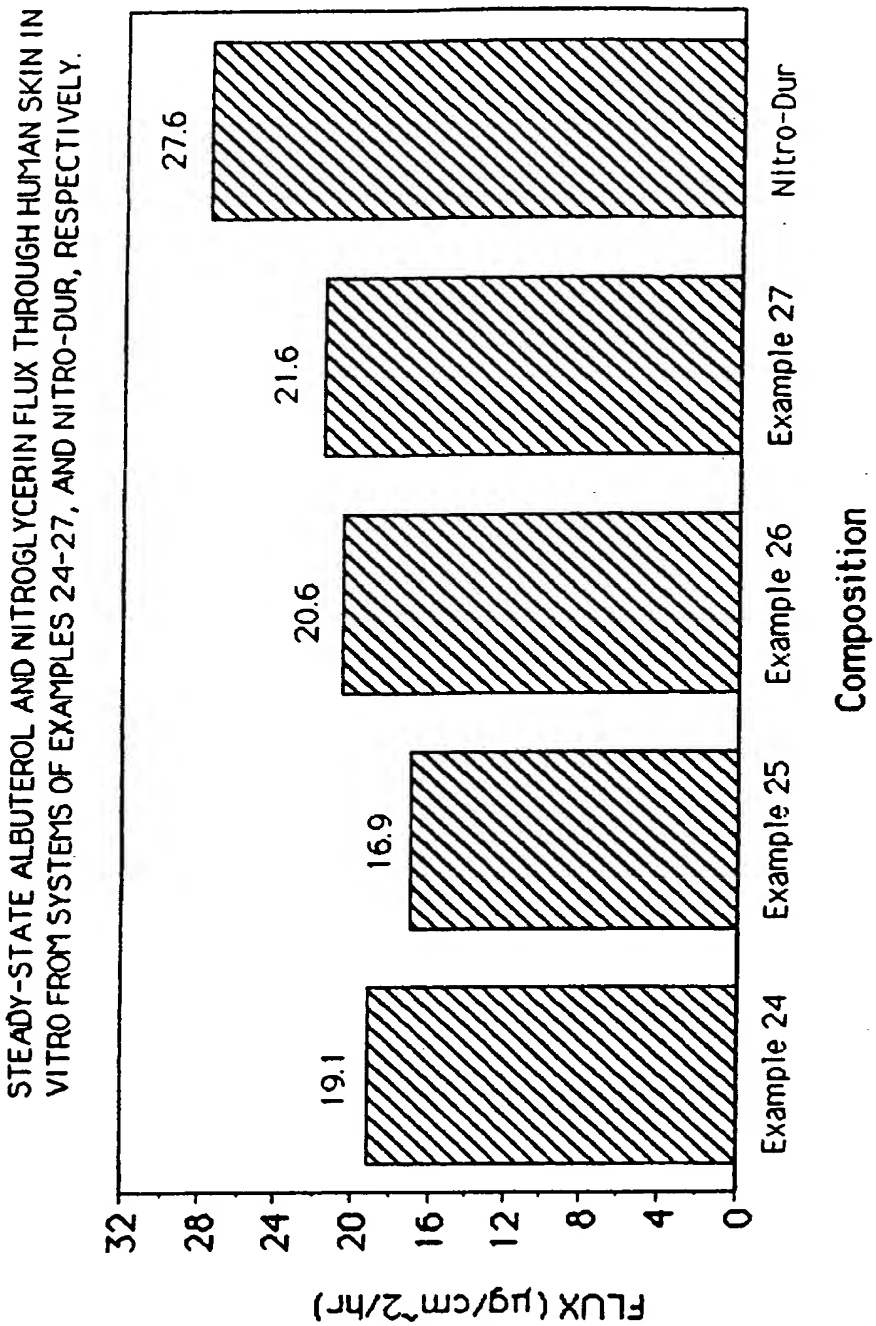

STEADY-STATE ALBUTEROL AND NITROGLYCERIN FLUX THROUGH HUMAN SKIN IN VITRO FROM SYSTEMS OF EXAMPLES 24-27, AND NITRO-DUR, RESPECTIVELY.
FLUX (µg/cm^2/hr)
0
4
8
12
16
20
24
28
32
19.1
16.9
20.6
21.6
27.6
Example 24
Example 25
Example 26
Example 27
Nitro-Dur
Composition

FIG. 11

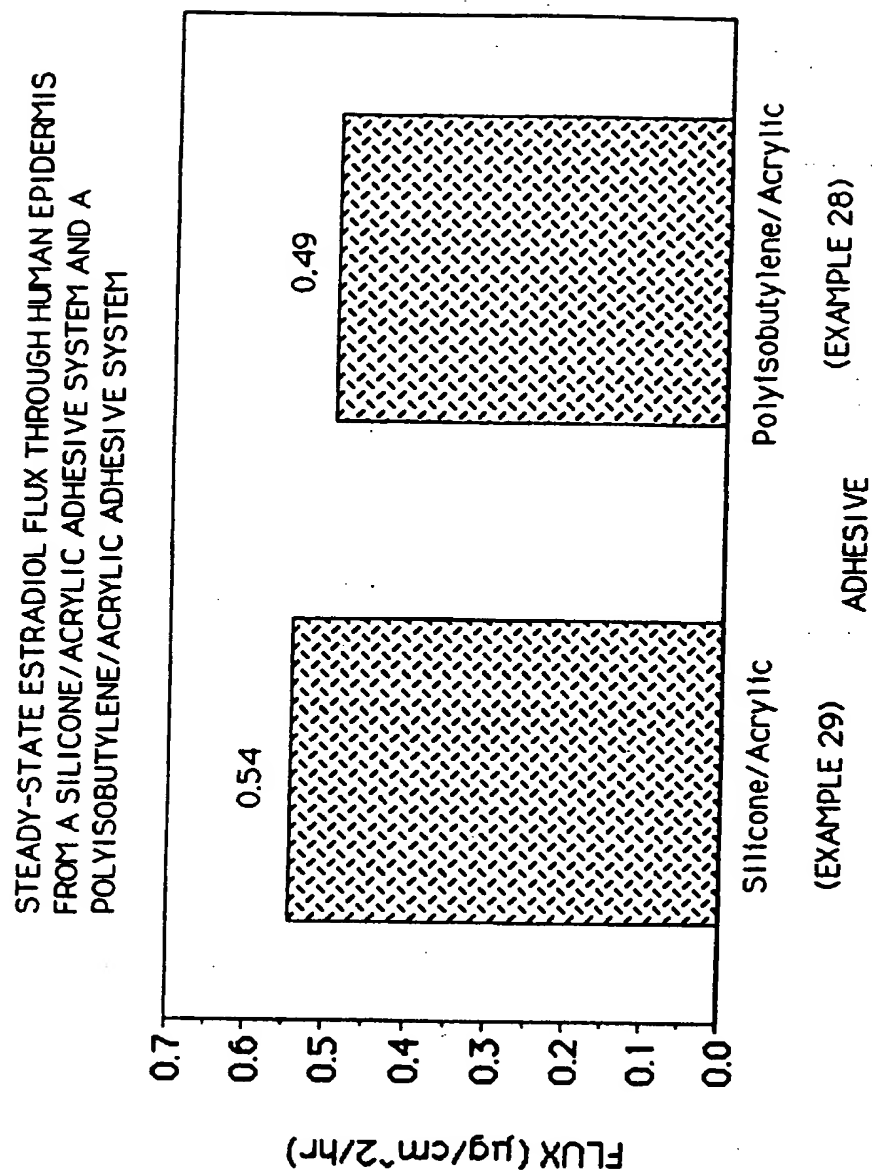

STEADY-STATE ESTRADIOL FLUX THROUGH HUMAN EPIDERMIS
FROM A SILICONE/ACRYLIC ADHESIVE SYSTEM AND A
POLYISOBUTYLENE/ACRYLIC ADHESIVE SYSTEM
FLUX (µg/cm^2/hr)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.54
0.49
Silicone/Acrylic
(EXAMPLE 29)
Polyisobutylene/Acrylic
(EXAMPLE 28)
ADHESIVE

FIG. 12

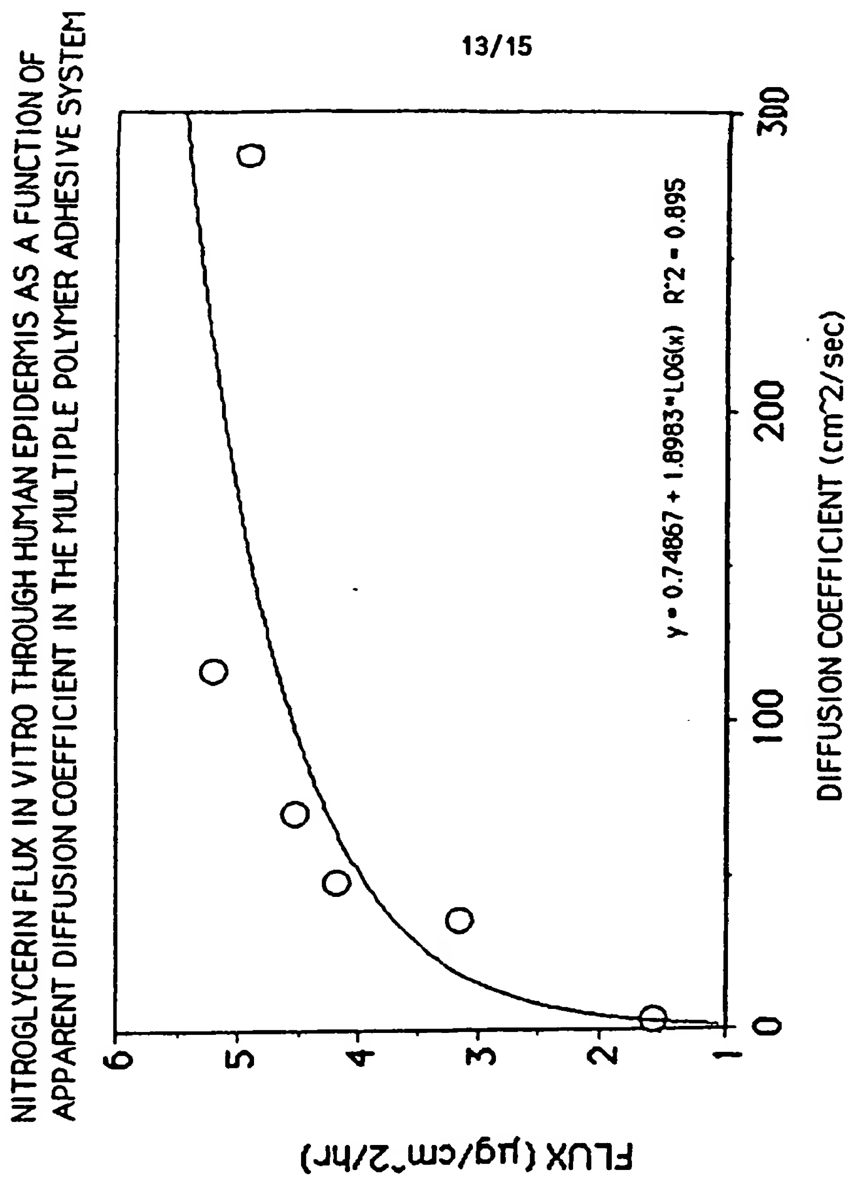

NITROGLYCERIN FLUX IN VITRO THROUGH HUMAN EPIDERMIS AS A FUNCTION OF
APPARENT DIFFUSION COEFFICIENT IN THE MULTIPLE POLYMER ADHESIVE SYSTEM
FLUX (µg/cm^2/hr)
6
5
4
3
2
1
0
100
200
300
y = 0.74867 + 1.8983*LOG(x) R^2 = 0.895
DIFFUSION COEFFICIENT (cm^2/sec)

FIG. 13

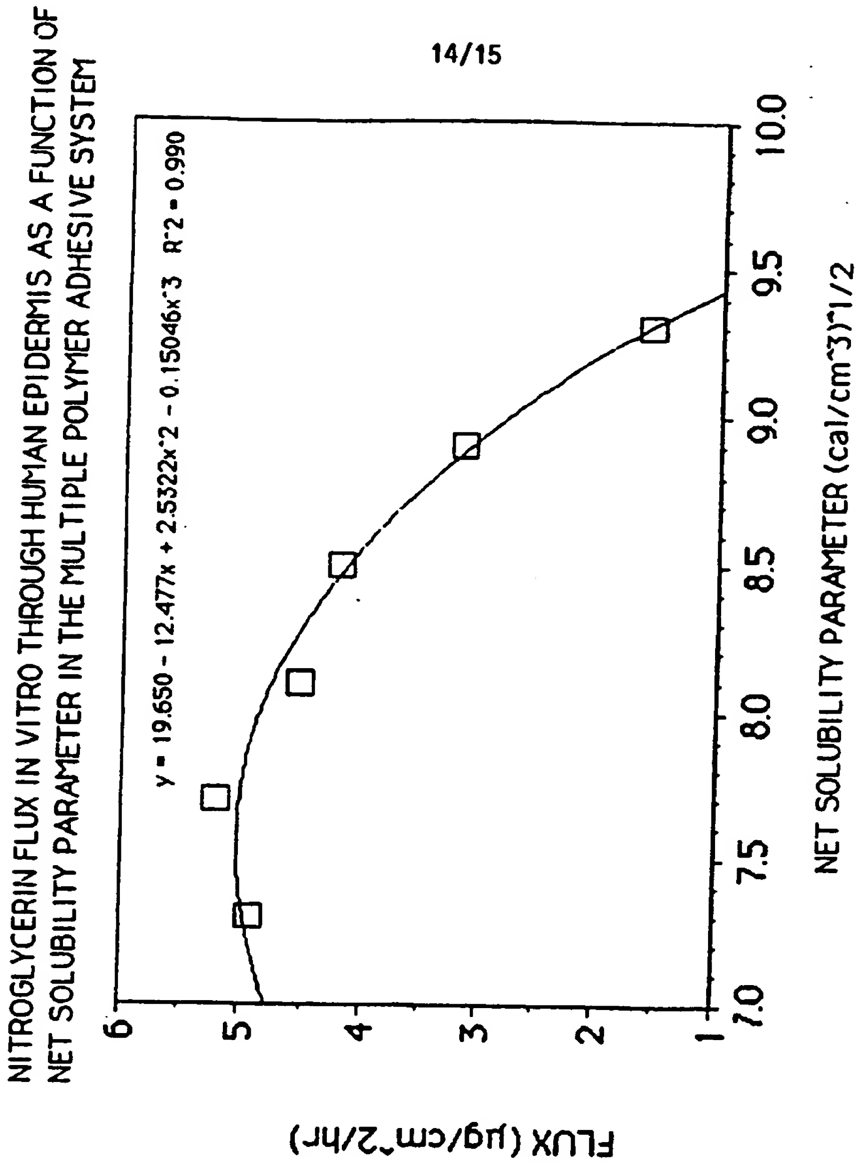

NITROGLYCERIN FLUX IN VITRO THROUGH HUMAN EPIDERMIS AS A FUNCTION OF NET SOLUBILITY PARAMETER IN THE MULTIPLE POLYMER ADHESIVE SYSTEM
y = 19.650 - 12.477x + 2.5322x^2 - 0.15046x^3 R^2 = 0.990
FLUX (µg/cm^2/hr)
6
5
4
3
2
1
7.0
7.5
8.0
8.5
9.0
9.5
10.0
NET SOLUBILITY PARAMETER (cal/cm^3)^1/2

FIG. 14

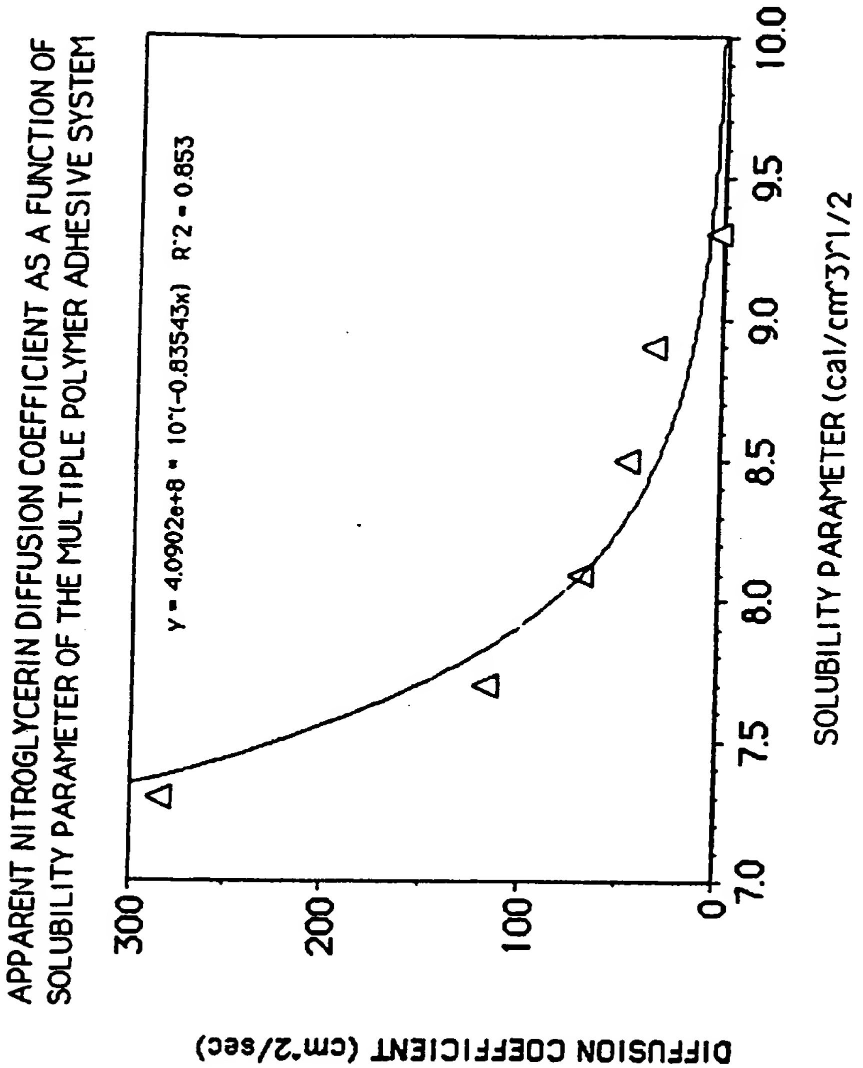

APPARENT NITROGLYCERIN DIFFUSION COEFFICIENT AS A FUNCTION OF
SOLUBILITY PARAMETER OF THE MULTIPLE POLYMER ADHESIVE SYSTEM
Y = 4.09902e+8 * 10^(-0.83543x)   R^2 = 0.853
DIFFUSION COEFFICIENT (cm^2/sec)
300
200
100
0
7.0
7.5
8.0
8.5
9.0
9.5
10.0
SOLUBILITY PARAMETER (cal/cm^3)^1/2

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61F 13/02, 13/00; A61L 15/16; A01N 37/00
US CL :421/448, 449, 447; 514/506
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 421/448,449,447;514/506

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

none

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 4,906,169 (Chien) 06 March 1990 See entire document.	1-15,21-44, 50-56, 72, 73,80-82, 101-106

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 13 AUGUST 1992	Date of mailing of the international search report 13 OCT [illegible]
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer LEON B. HORNE
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05297

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 16-20, 45-49, 57-71, 74-79 & 83-100
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addtional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention frist mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 524 776 B1**

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(45) Date of publication of patent specification: **23.08.95**

(51) Int. Cl.[6]: **C09J 183/04, A61K 9/70, A61L 25/00, C09J 183/10**

(21) Application number: **92306544.5**

(22) Date of filing: **16.07.92**

(54) **Silicone pressure sensitive adhesive compositions for transdermal drug delivery devices and related medical devices.**

(30) Priority: **22.07.91 US 733497**

(43) Date of publication of application:
27.01.93 Bulletin 93/04

(45) Publication of the grant of the patent:
23.08.95 Bulletin 95/34

(84) Designated Contracting States:
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(56) References cited:
EP-A- 0 156 080
EP-A- 0 224 981
WO-A-91/09633
FR-A- 1 546 983

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EP 0 524 776 B1

Description

This invention relates to silicone pressure sensitive adhesive compositions having improved cohesive strength and stability and transdermal-type drug delivery devices and related medical devices for using the compositions.

A pressure sensitive adhesive is generally a material which adheres to a surface with slight pressure and releases from the surface with negligible transfer of the adhesive to the surface. The most common examples are the adhesives used in bandages to cover wounds. Silicone pressure sensitive adhesives in particular have found use in transdermal drug delivery applications which involve the adherence of a drug-containing patch to a patient's skin, due to the fact that silicone pressure sensitive adhesives are acceptable for topical use.

In transdermal drug delivery patches, ingredients such as co-solvents and excipients have been added to the silicone pressure sensitive adhesive compositions to improve efficacy. Co-solvents are typically added to increase drug solubility in the composition and excipients are typically added to enhance drug release from or through the composition.

However, when silicone pressure sensitive adhesives are formulated with or come in contact with co-solvents, excipients, drugs such as nicotine-based drugs or skin penetration enhancers such as propylene glycolmonolaurate or glycerol monoleate, the silicone pressure sensitive adhesive often becomes plasticized, losing tack, adhesiveness and resistance to flow. Such instances occur (1) in matrix-type drug delivery patches where a drug is formulated into a silicone pressure sensitive adhesive and (2) in reservoir-type drug delivery patches where a silicone pressure sensitive adhesive is on the surface of a drug delivery device containing a reservoir of a drug. In the former type of patch, the silicone pressure sensitive adhesive is in intimate contact with the drug and other possible plasticizing additives. In the latter type of patch, the silicone pressure sensitive adhesive is present to provide means for attaching the device to a patient's skin. In this device, drugs or other materials from the reservoir either pass through or otherwise may come in contact with the silicone pressure sensitive adhesive.

The problem with either device is that the additives cause reduction in cohesive strength. Cohesive strength causes the adhesive to adhere to a substrate such as a patch and prevents flow or transfer of the pressure sensitive adhesive onto either the release liner which protects the silicone pressure sensitive adhesive before use or onto the patient's skin following removal of the patch while maintaining adequate adhesion of the patch to the skin. The cohesive strengthening agent further prevents flow of the pressure sensitive adhesive beyond the edges of the patch during storage and/or use.

It is, therefore, a primary object of the invention to provide a pressure sensitive adhesive composition which has good cohesive strength and is resistant to cold,flow when formulated or contacted with drugs, o-solvents, excipients or skin penetration enhancers.

A silicone pressure sensitive adhesive composition which meets the object of the invention is disclosed which is compatible with drugs, excipients, co-solvents and skin penetration enhancers while allowing for the addition of a cohesive strengthening agent to reduce cold flow. The silicone pressure sensitive adhesive comprises a silicone fluid, a silicate resin and a cohesive strengthening agent. By the addition of a cohesive strengthening agent, an improved silicone pressure sensitive adhesive is produced which retains the adhesive on the substrate, without compromising the adhesion of the adhesive to the skin of the patient wearing the bandage or patch.

In meeting the object of the invention, a silicone pressure sensitive adhesive includes a cohesive strengthening agent selected from the group consisting of nonionic surfactants, fatty acid esters of glycerol, said nonionic surfactants and said fatty acid esters being substantially insoluble in said mixture, as well as solid particulate materials selected from the group consisting of metallic salts of fatty acids, metallic salts of phosphoric acid, metallic salts of carbonic acid, polysaccharides, carboxy-polymethylene, polyvinylpyrrolidone, polyvinylalcohol and amorphous precipitated silicas having a surface area of less than approximately 200 m^2/g and between 10 and 200 m^2/g.

The nature and extent of the present invention will be clear from the following detailed description of the particular embodiments thereof, taken in conjunction with the appendant drawings, in which:

FIGURE 1 shows a pressure sensitive adhesive sandwiched between a backing substrate and a release liner;

FIGURE 2 shows a matrix-type delivery device for a bioactive agent or drug in place within a transdermal patch;

FIGURE 3 shows a liquid reservoir-type transdermal drug delivery device; and

FIGURE 4 shows a solid state reservoir-type transdermal drug delivery device.

Generally, the silicone pressure sensitive adhesive compositions of the present invention include a silicone pressure sensitive adhesive containing (i) a silicone fluid, (ii) a silicate resin and (iii) a cohesive strengthening agent. The silicone pressure sensitive adhesive of the present invention includes a cohesive strengthening agent in order to overcome the problems of excessive cold flow or creep presented by the pressure sensitive adhesives of the prior art. Cold flow or creep refer to viscoelastic flow of the adhesive solids under stress. Resistance to cold flow is referred to as creep resistance. This is defined by, Carl A. Dahlquist, "Creep", Handbook Of Pressure Sensitive Adhesive Technology 2nd ed., (Van Nostrand Runhold, New York, N.Y., 1989), p. 97. As can be seen by the test results of the examples below, the addition of the cohesive strengthening agents of the present invention substantially reduces cold flow. By reducing the cold flow, a superior product can be made which keeps the adhesive more on the bandage or patch, with less of the adhesive transferring to the skin of the patient wearing the bandage or transdermal patch without compromising the adhesion of the bandage to the skin of the patient. As one can remember, previous bandages left a sticky residue on the skin when it was removed. This invention alleviates this problem substantially.

One suitable class of silicone pressure sensitive adhesives which may be employed in the silicone pressure sensitive adhesive compositions of this invention consists of a mixture of (i) a silanol end-blocked polydiorganosiloxane fluid, e.g. a polydimethylsiloxane polymer and (ii) a trimethylsilyl end-blocked polysilicate resin such as a silicate resin consisting of a benzene-soluble resinous copolymer containing silicon-bonded hydroxyl radicals and consisting essentially of triorganosiloxy units of the formula $R_3SiO_{1/2}$ and tetrafunctionalsiloxy units of the formula $SiO_{4/2}$ in a ratio of 0.6 to 0.9 triorganosiloxy units for each tetrafunctionalsiloxy unit present in the copolymer, wherein each R is a monovalent organic radical independently selected from the group consisting of hydro-carbon radicals of from 1 to 6 inclusive carbon atoms. U.S. Patent No. 2,736,721 to Dexter et al. and U.S. Patent No. 2,814,601 to Currie et al. teach such or similar silicone pressure sensitive adhesives.

Another class of suitable silicone pressure sensitive adhesives for use according to this invention is that or those similar to U.S. Patent No. 2,857,356, to Goodwin, Jr. The Goodwin, Jr. patent teaches silicone pressure sensitive adhesives which consist of a mixture of ingredients comprising (i) a cohydrolysis product of a trialkyl hydrolyzable silane and alkyl silicate, wherein the cohydrolysis product contains a plurality of silicon-bonded hydroxy groups and (ii) a linear, high viscosity organo-polysiloxane fluid containing silicon-bonded hydroxy groups.

The silicone fluid and the silicate resin may optionally be condensed together according to a procedure such as the procedure described in Canadian Patent No. 711,756 to Pail. In such a condensation reaction, the silicate resin and the silicone fluid are mixed together in the presence of a catalytic amount of a silanol condensation catalyst and then the silicate resin and the silicone fluid are condensed, for example, by heating under reflux conditions for 1 to 20 hours. Examples of silanol condensation catalysts are primary, secondary and tertiary amines, carboxylic acids of these amines and quaternary ammonium salts.

Another class of suitable pressure sensitive adhesives to use according to the invention are those compositions described in U.S. Patent Nos. 4,591,622 and 4,584,355 to Blizzard et al., U.S. Patent No. 4,585,836 to Homan et al. and U.S. Patent No. 4,655,767 to Woodard et al. Generally, these pressure sensitive adhesives consist of a blend of (i) a silicate resin and (ii) a silicone fluid which are chemically treated to reduce the silicon-bonded hydroxyl content of the blend. These adhesives may optionally be condensed as described immediately above prior to the chemical treatment.

In addition, the various types of silicone pressure sensitive adhesives may be blended to achieve blended characteristics. Preferably, for the greatest improvement in cohesive-strength, the silicone pressure sensitive adhesive contains some silanol radicals, preferably greater than 200 ppm and, more preferably, greater than 400 ppm.

Typically, the most practical pressure sensitive adhesive for use in this invention includes a high molecular weight polydimethylsiloxane as the silicone fluid, since this fluid is the most economical and the most readily available of the silicone fluids. The ratio of polydimethylsiloxane polymer to silicate resin, is 30 parts to 70 parts by weight based on total adhesive composition weight.

The other adhesive component, the silicate resin, preferably has a molecular weight ranging from 2,000 to 4,000. The resin is employed in amounts from 40 to 70 parts by weight in the silicone pressure sensitive adhesive, while the silicone fluid is employed from 60 to 30 parts by weight, wherein the total parts of the silicate resin and the silicone fluid equal 100 parts. The silicone pressure sensitive adhesive composition contains no less than 100 ppm of silanol radicals and preferably contains between 200 ppm and 1200 ppm of silanol radicals.

The silicone pressure sensitive adhesive compositions of this invention may also contain the aforementioned ingredients: drugs, co-solvents, excipients, skin penetration enhancers or organic solvents for

dissolving the silicone polymer and the silicate resin. Suitable organic solvents may have reinforcing excipients dispersed therein for dissolving the polydimethylsiloxane polymer and silicate resin and should have a Hildebrand solubility parameter ranging from between 10.2 to 20.5 $J^{1/2}/cm^{3/2}$ (5 to 10 $cal^{1/2}/cm^{3/2}$) and, optimally, between 16.4 to 18.4 $J^{1/2}/cm^{3/2}$ (8 and 9 $cal^{1/2}/cm^{3/2}$). Examples of suitable organic solvents include aromatics such as toluene and xylene; aliphatics such as heptane and hexane; chlorinated solvents such as 1,1,1-trichloroethane and trichlorotrifluoroethane; fluorocarbons such as Freon 113 (Freon PCA) available from DuPont de Nemours, E.I. Co., Wilmington, DE; aliphatic esters such as ethyl acetate and mixtures thereof.

The silicone pressure sensitive adhesives used in this invention are not considered to be silicone adhesives which are "silicone rubbers", which generally refer to non-tacky vulcanized rubber used as structural adhesives. The most common type of silicone rubber consists of a mixture of a polydimethysiloxane gum, a filler (such as fumed silica or other inorganic, non-resinous material), a crosslinker and, optionally, a catalyst. These structural adhesives are cured to a fully rubberized state. The silicone pressure sensitive adhesives employed in this invention are tacky (or sticky) to the touch without the addition of plasticizers and typically adhere to a substrate after mild pressure is applied and therefore are referred to as pressure sensitive adhesives. The silicone pressure sensitive adhesives may be cured or "rubberized" after being mixed with the cohesive strengthening agent as discussed below. However, even after the curing, the silicone pressure sensitive adhesive composition remains tacky.

The process of curing or crosslinking silicone pressure sensitive adhesives is known in the art. For example, see "Silicone Pressure Sensitive Adhesives" by D.F. Merrill in the Handbook Of Pressure Sensitive Adhesive Technology, edited by D. Satas (Van Nostrand Reinhold, Florence, Kentucky, 1982), pages 344-352 and "Formulating Silicone Pressure Sensitive Adhesives For Application Performances" by L.A. Sobieski in Making It Stick in '86, Advances In Pressure Sensitive Tape Technology, seminar proceedings (Pressure Sensitive Tape Council, Deerfield, Illinois, 1986), pages 1-5.

Generally, however, for drug delivery applications, the silicone pressure sensitive adhesive compositions are not crosslinked because either (1) the crosslinking temperature is too high for the drugs or (2) the additives needed for crosslinking are non-biocompatible ingredients. A silicone pressure sensitive adhesive composition is generally considered not crosslinked if it can he dissolved in a solvent.

Another difference between silicone pressure sensitive adhesives suitable for use in the present invention and unsuitable silicone rubbers lies in the fact that silicone pressure sensitive adhesives are usually fillerless or contain low amounts, e.g., less than 5 weight %, of fillers, such as fumed silica or other inorganic reinforcing fillers known in the silicone art. On the other hand, silicone rubbers typically contain 15-35 weight % filler. Fillers are usually not desired in high quantities in silicone pressure sensitive adhesives, because high quantities often cause the silicone pressure sensitive adhesives to lose tack and adhesiveness and to increase in viscosity, making it more difficult to apply a coating of the silicone pressure sensitive adhesive.

The cohesive strengthening agents utilized in the invention are generally insoluble in an adhesive polymer or solution and have a mean particle size ranging from 0.5 to 100 µm. The melting point for the cohesive strengthening agents should be greater than about 100 °C. Specifically, the cohesive strengthening agents useful for the present invention include those selected from the group consisting of: 1) nonionic surfactants; 2) fatty acid esters of glycerol; and solid particulate materials selected from the group consisting of 3) metallic salts of fatty acids; 4) metallic salts of phosphoric acid; 5) metallic salts of carbonic acid; 6) polysaccharides; 7) carboxypolymethylene; 8) polyvinylpyrrolidone; 9) polyvinylalcohol; and 10) amorphous precipitated silicas having a surface area of between 10 and 200 m^2/g, with a particle size range of between .018 and 100 µm. These cohesive strengthening agents are individually described below.

Nonionic surfactants which are useful as the cohesive strengthening agent include those that are not generally soluble in the silicone pressure sensitive adhesives. Thus, they form a two-phase composition when mixed with the silicone pressure sensitive adhesive. In particular, nonionic surfactants having a hydrophilic-lipophilic balance (HLB) of between 7 and 14 are suitable. A specific example of such a surfactant is nonylphenoxypoly(ethyleneoxy)ethanol, an ethoxylated alkyl phenol that conforms generally to the formula:

$$C_9H_{19}C_6H_4(OCH_2CH_2)_nOH$$

where n has an average value of 9 and is sold under the trademark IGEPAL Co-630, which is owned by GAF Chemicals Corp., and is available from GAF Chemicals Corp, of Wayne, N.J. 07470. IGEPAL, Co-630 has an HLB value of about 13.

Fatty acid esters of glycerol useful as the cohesive strengthening agent generally have a high polarity and are also substantially insoluble in silicone pressure sensitive adhesives. Examples of such fatty acid esters of glycerol include cottonseed oil, corn oil, peanut oil, sesame oil and coconut oil. These oils are oily liquids at room temperature with the exception of coconut oil which is semi-solid at room temperature.

Examples of metallic salts of fatty acids which have been found suitable as cohesive strengthening agents include calcium stearate, magnesium stearate and sodium stearate. A suitable calcium stearate is Calcium Stearate RSN[R] 11-4, commercially available from Mallinckrodt Inc, St. Louis, MO 63147, which contains about 9-10.5 weight percent calcium oxide, has a particle size from 1.7 to 60 μm and a specific surface area from 5.76 to 7.44 m^2/g. A suitable magnesium stearate is commercially available from Mallinckrodt Inc., St. Louis, MO 63147 and has a specific surface area from 2.45 - 7.93 m^2/g. Calcium stearate is the preferred stearate of the three stearates due to its performance in increasing cohesive strength of the silicone pressure sensitive adhesive.

Metallic salts of phosphoric and carbonic acid. The preferred metallic salt of phosphoric acid includes dibasic calcium phosphate, while the preferred metallic salt of carbonic acid is calcium carbonate.

Examples of polysaccharides which are useful as cohesive strengthening agents in the present invention include celluloses, xanthan gum, pectin, guar gum and karaya gum. Polysaccharides contain hydroxyl radicals which are believed to be useful for bonding with the silanol radicals of the silicone pressure sensitive adhesives. Suitable polysaccharides may be celluloses which can include micro-crystalline cellulose, powdered cellulose, methylcellulose, ethylcellulose, sodium carboxymethylcellulose. Micro-crystalline cellulose has the general formula $(C_6H_{10}O_5)_n$, where n is 220, with a molecular weight of 36,000, an average particle size of 20 to 100 μm and a specific surface area from 10 to 21 m^2/g. Powdered cellulose has the general formula of $(C_6H_{10}O_5)_n$, where n is 1500, with a molecular weight of 243,000 and a particle size of from 1 to 250 μm. Methylcellulose is a long chain substituted cellulose ether of 50-1500 anhydroglycose units containing 26-32% methoxyl groups.

Another cohesive strengthening agent thought to be useful is carboxypolymethylene is also known as "carbomer". Generally, it is a cross linked polymer of acrylic acid having 0.75-2.0 weight percent polyalkylsucrose having the empirical formula: $(C_3H_4O_2)_x.(C_3H_5\text{-sucrose})_y$ with molecular weights from 1×10^6 to 4×10^6.

Polyvinylpyrrolidones are also thought to be useful as the cohesive strengthening agent. They generally have the empirical formula $(C_6H_9NO)_n$, with a mean molecular weight from 10,000 to 700,000.

Furthermore, polyvinylalcohols may be useful as the cohesive strengthening agent, having the empirical formula $(C_2H_4O)_n$, with an average molecular weight of from 30,000 to 200,000 and a melting point of 228 °C.

Amorphous precipitated silicas which have been found to be especially suitable as the cohesive strengthening agents of this invention include amorphous precipitated silicas having a surface area of between 10 and 200 m^2/g and a particle size ranging from 0.018 to 100 μm. One such commercially available silica is "SILENE" 732D, available from PPG Industries, Inc., Pittsburgh, PA., owner of the trademark "SILENE". "SILENE" 732D is an amorphous precipitated hydrated silica product which typically contains about 88 weight percent silica on a dry basis and about 7 weight percent water, with an average particle size of .072 μm, a BET surface area of 30 m^2/g and a pH of from 8.5 to 9.

Generally, the cohesive strengthening agents are insoluble in the silicone pressure sensitive adhesive, thus forming a dispersion or suspension of cohesive strengthening agent microparticles in the adhesive matrix. In addition, they are approved pharmaceutical additives. Many of the cohesive strengthening agents have the ability to hydrogen-bond to the silanol radicals of the silicone pressure sensitive adhesive due to the presence of carboxyl or hydroxyl radicals on the cohesive strengthening agents. Tests have shown that the cohesive strengthening agents of the present invention increase the viscosity of the silicone pressure sensitive adhesive at room temperature.

When mixed with the silicone fluid and silicate resin to practice this invention, the cohesive strengthening agents are desirably employed from between 1.0 to 20.0 weight percent and, more desirably, from 5.0 to 15.0 weight percent based on the total weight of the silicone pressure sensitive adhesive composition. The three main components of this invention may be made by mixing the ingredients in any order. However, reaction or treatment of the ingredients, e.g., condensing according to the procedure of the previously-mentioned Pail patent or chemically treating according to the previously mentioned Blizzard et al., etc. patents, may require completion prior to the addition of the cohesive strengthening agent.

Referring now to the drawings, Figure 1 illustrates a tape including a silicone pressure sensitive adhesive generally denoted by the numeral 10 which comprises a backing substrate 12, a pressure sensitive adhesive layer 14 and a release liner 16. This figure illustrates the basic configuration of a tape with a pressure sensitive adhesive made in accordance with the present invention. Possible uses for this

embodiment are for bandages, wound dressings and medical transfer tapes. Hereinbelow are described more embodiments, with reference to the other figures.

With reference to the remaining drawings, the silicone pressure sensitive adhesive compositions of this invention are especially suitable for assisting in delivering a bioactive agent, such as a drug, to a bioactive agent-accepting substrate, such as a patient's skin. The silicone pressure sensitive adhesive compositions of this invention may be employed in three types of bioactive agent delivery modes. The first mode is a matrix-type of delivery device for the bioactive agent or drug. The matrix-type delivery device is usually a dermal patch which delivers the bioactive agent locally.

As shown in Figure 2, this matrix-type delivery device is generally shown as 20 and comprises at least three layers. The first layer is a backing substrate 22 which may be permeable or occlusive to water vapor transmission from skin. The second layer is a matrix 24 atop at least portions of the backing substrate. The matrix may be one of two embodiments. In a first embodiment, as shown in Figure 2, the matrix is made up of the silicone, creep resistant, pressure sensitive adhesive. The adhesive matrix may contain and is compatible with compositions selected from the group consisting of drugs, excipients, enhancers, co-solvents and mixtures thereof, shown at 26. In a second embodiment (not shown) the matrix is made up of a polymer. The polymer matrix may contain and is compatible with compositions selected from the group consisting of drugs, excipients, enhancers co-solvents and mixtures thereof. In this second embodiment, the silicone, creep-resistant, pressure sensitive adhesive is disposed in a layer atop at least portions of the polymer matrix. The matrix is between about 1 and about 15 mils thick. The final layer is a pressure sensitive adhesive release liner 28 contacted on the matrix. The liner is between 25.4 and 381 μm (1 and 15 mils) thick and preferably between 127 and 254 μm (5 and 10 mils) thick.

The matrix-type drug delivery device as shown in Figure 2 may include various drugs selected from the group consisting of cardiovascular agents, antiarrthymic agents, antianginal agents, antibiotics, antifungals, antimicrobials, antihypertensives, analgesics, local anesthetics, contraceptives, hormonal supplements, anti-smoking agents, appetite suppressants, hypnotics, anxiolytics and mixtures thereof. Also included may be co-solvents, enhancers and excipients selected from the group consisting of fatty acid esters, polyols, surfactants, terpenes, glycerol esters, polyethylene glycol esters, amides, sulfoxides, lactams, nonionic surfactants, sorbitan esters and mixtures thereof.

As shown in Figures 3 and 4, the second mode of delivery is a reservoir-type transdermal drug delivery device. Generally, this mode is applied to the skin to deliver the bioactive agent to treat systemic disease. Figure 3 shows a liquid containing reservoir-type drug delivery device generally denoted as numeral 30 which comprises a minimum of five layers from top to bottom. The first layer 32 is a backing substrate. The second layer 34 includes a liquid reservoir which may contain bioactive agents or other compositions selected from the group consisting of drugs, excipients, enhancers, co-solvents and mixtures thereof. The reservoir-type transdermal drug delivery device as shown in Figure 3 may include various drugs selected from the group consisting of cardiovascular agents, antiarrthymic agents, antianginal agents, antibiotics, antifungals, antimicrobials, antihypertensives, analgesics, local anesthetics, contraceptives, hormonal supplements, anti-smoking agents, appetite suppressants, hypnotics, anxiolytics and mixtures thereof. Also included may be co-solvents, enhancers and excipients selected from the group consisting of fatty acid esters, polyols, surfactants, terpenes, glycerol esters, polyethylene glycol esters, amides, sulfoxides, lactams, nonionic surfactants, sorbitan esters and mixtures thereof. The third layer 36 is a rate controlling membrane positioned such that the reservoir 34 is sealed between the backing substrate 32 and the rate controlling membrane 36. This membrane acts as the rate controlling mechanism for the delivery of the liquid drug(s), co-solvents, enhancers and excipients, from the reservoir 34. The fourth layer 38 is a pressure sensitive adhesive which should be compatible with any of the drugs, excipients and co-solvents present in the liquid reservoir. The fifth layer 40 is a silicone pressure sensitive adhesive release liner. The release liner is between 25.4 and 381 μm (1 and 15 mils) thick and preferably between 25.4 and 76.2 μm (1 and 3 mils) thick. The bioactive agent of the liquid reservoir 34 may then pass from the reservoir through the attached rate controlling membrane 36 and the adhesive layer 38 and then into the skin of the patient to deliver the drug.

Figure 4 shows a solid state reservoir-type transdermal drug delivery device. This device is denoted generally by numeral 50 and includes a first layer 52 which is a backing substrate. The second layer constitutes a solid reservoir 54 which may contain one or more bioactive agents of other compositions selected from the group consisting of drugs, excipients and co-solvents indicated at 56. The same drugs, excipients and co-solvents may be used as the liquid containing reservoir as shown in Figure 3. The third layer of Figure 4 is a pressure sensitive adhesive layer 58 which is compatible with the drugs, excipients and co-solvents. The fourth layer is a release liner 60. The liner 60 averages between 25.4 and 381 μm (1 and 15 mils) thick and is preferably between 25.4 and 76.2 μm (1 and 3 mils) thick. An additional layer (not

shown) comprising a rate controlling membrane may be positioned between the solid reservoir 54 and the adhesive 58 in order to control the rate of delivery of the drug(s) and excipient(s). The surface area of both the matrix-type and reservoir-type delivery device generally ranges between 1.0 and 700 cm^2. This range is not to be construed as limiting, as any size device may utilized with the PSA of the present invention.

The adhesive layer of both the matrix-type and reservoir-type delivery devices, shown in Figures 2-4, may include one or a combination of co-solvents, enhancers and excipients which increase solubility of the drug in the adhesive matrix, enhance skin permeation to the drug or enhance drug release from the system.

The presence of the cohesive strengthening agents in the adhesives of the present invention permits the use of drugs, excipients, co-solvents and skin penetration enhancers which usually adversely effect the cohesive strength of prior art silicone pressure sensitive adhesives not containing any cohesive strengthening agents. Preferably, the cohesive strengthening agents have a melting point of greater than 40 °C. and a Hildebrand solubility parameter between 10.2 to 30.7 $J^{1/2}/cm^{3/2}$ (5 and 15 $cal^{1/2}/cm^{3/2}$). The addition of the cohesive strengthening agents taught herein significantly reduces flow and improves creep resistance of silicone adhesives utilized to deliver a bioactive agent, such as a drug to a substrate, such as a patient's skin.

The following examples of the invention are meant to be illustrative only and should not be construed as limiting the invention which is properly delineated in the appended claims. In the following examples, all parts and percentages are by weight unless otherwise specified.

The basic silicone pressure sensitive adhesive prepared without the cohesive strengthening agent may be prepared as follows. Once this basic formulation was prepared, Examples A-F were made by adding various cohesive strengthening agents, testing them and tabulating the results.

The basic adhesive formulations include two main components: a silicate resin and a silicone fluid. In this preparation, we will be discussing Adhesives I, II and III. They are made from various combinations of Resins A-1, A-2 and trimethylsiloxy end-blocked polydimethylsiloxane (PDMS) Fluid A as described below.

Resin A-1 is a xylene solution of a resinous copolymeric siloxane prepared from 45 parts of sodium silicate and 20 parts of Me_3SiCl ($Me = CH_3$) according to the method of U.S. Patent No. 2,676,182 to Daudt et al. and contains $Me_3SiO_{1/2}$ units and $SiO_{4/2}$ units in a ratio of approximately 0.75:1.0 and has a nonvolatile content typically about 69-71%, an acid number in the range of 0.3 to 1.4, a viscosity in the range of 10-14 mPa•s (10-14 centipoise) at 25 °C. in hexane solution and a silicon-bonded hydroxyl content of about 2.5 weight percent based on a 100% non-volatilized content and a number average molecular weight range of between 2,000 to 4,000.

Resin A-2 is Resin A-1 which has been devolatilized (100% non-volatile content).

PDMS Fluid A is a homogeneous mixture of a hydroxyl end-blocked polydimethylsiloxane having a number-average molecular weight range of between 40,000 to 100,000 with minor amounts of cyclic polydimethylsiloxane having degrees of polymerization between 4 and 30, the mixture having a viscosity between 12,000 and 15,000 mPa•s (centipoise) as measured using a Brookfield Viscometer Model HAF with spindle #3 at 10 RPM's.

Adhesive I, a 50 wt% solution of a high silanol containing silicone pressure sensitive adhesive in xylene solvent was prepared by homogeneously mixing 34.0 parts by weight of Resin A-2, 34.0 parts by weight xylene and 31.0 parts by weight PDMS Fluid A. The mixture was then heated to 100 °C. and anhydrous ammonia was passed through the mixture at a rate of 5 ml/min/kg (11 ml/min/lb) of non-volatile component of the mixture for approximately 2 hours. The mixture was then stripped to greater than 99% non-volatile content and redissolved in hexane to a non-volatile content of 50 wt%.

Adhesive II, a 50 wt% solution of a low silanol containing silicone pressure sensitive adhesive in xylene solvent, was prepared by homogeneously mixing 34.0 parts by weight of Resin A-2, 34.0 parts by weight hexane and 31.0 parts by weight PDMS Fluid A. The mixture was then heated to 100 °C. and anhydrous ammonia was passed through the mixture at a rate of approximately 5 ml/min/kg (11 ml/min/lb). of nonvolatile component of the mixture for approximately 2 hours. To endcap the mixture, hexamethyldisilazane was then admixed at a 3:1 mole ratio of end-blocking triorganosilyl to total silicon-bonded hydroxyl radicals present in the resin copolymer and polydiorganosiloxane and the mixture was allowed to react for 3 hours at 95-100 °C. The mixture was then heated to 140 °C. and maintained at 140 °C. under reflux conditions for 3 hours to remove condensation water. The mixture was then stripped to greater than 99% non-volatile contents and redissolved in hexane to a non-volatile content of 50 wt%.

Adhesive III, a 50 wt% solution of a high silanol-containing silicone pressure sensitive adhesive in Freon PCA solvent was prepared as described for Adhesive I, except, after stripping, it was redissolved in Freon PCA to a non-volatile content of 50 wt%.

Preferably, the silicone pressure sensitive adhesives formed by this invention have tack values ranging between 50 and 800 grams; peel values between 0.5 and 50 g/cm; adhesion values between about 200 and

2000 g/cm; a dynamic viscosity of between 1 x 10^4 and 1 x 10^7 Pas (1 x 10^5 and 1 x 10^8 poise); loss modulus between 1 x 10^4 and 1 x 10^6 N/m^2 (1 x 10^5 and 1 x 10^7 dyne/cm^2) and a loss tangent between about 0.2 and 1.0 at a sweep frequency of 1 rad/sec on a 1mm thick sample at room temperature.

Creep was also measured. As stated hereinabove, creep is a measure of viscoelastic flow of the adhesive solids.

A general method for measuring the values for tack, peel force and adhesion is described here. Although the following examples utilize different chemical compositions, the following testing methods were followed for all samples. Measurements were obtained through testing a one inch wide polyester tape having a silicone pressure sensitive adhesive thereon prepared by blending about 5 percent calcium stearate with about 90% by weight solution of silicone pressure sensitive adhesive and casting it to a 127 µm (5 mil) thickness on "SCOTCHPAK" 1022 Release Liner, a polyester film coated with a release coating available from the 3M Company, St. Paul, Minnesota, owner of the trademark "SCOTCHPAK", 3M Company Health Care Specialties Div. St. Paul Minnesota. After coating, a sheet strip of "MYLAR" polyester film, 127 µm (5 mils) thick, is adhered to each coated sample with a 2.0 kg (4.5 lb). rubber transfer roller. Laminated sheets were then cut into 25.4 mm (1 inch) wide strips.

The tack values were measured using a "POLYKEN" Probe Tack Tester, Series 400, made by Testing Machines, Inc., Amityville, NY. The speed of the probe was controlled at 1.0 cm/second and the dwell time of the probe was 1.0 seconds. Tack values of between 50 and 800 grams are considered acceptable. Test results for the tack values of this Example of a calcium stearate containing adhesive are set forth in Table C2 and range between 144 (+/- 16) grams and 182 (+/- 84) grams, well within the desirable range.

Peel values were obtained by stripping the tape from the "SCOTCHPAK" 1022 Release Liner at a rate of 17 mm/sec (40 inches/minute) at an angle of 180^0 while attached to a tensile testing machine. An average value over the entire length of the liner was recorded. Peel values of less than 50 g/cm were considered acceptable. These peel values are set forth in Table C2 and were between 0.70 (+/-0.20) and 4.50 (+/-0.10) g/cm for all samples, again, within the acceptable values of less than 50 g/cm.

Adhesion values were obtained as follows. The calcium stearate containing silicone pressure sensitive adhesive composition was adhered to a stainless steel panel with a 2.0 kg (4.5 lb). roller and allowed to equilibrate for 15 minutes. The adhesion measurements were obtained by stripping each tape from the panel at a rate of 5.1 mm/sec (12 inches/minute) at an angle of 180^0 while attached to a tensile testing machine. Adhesion values were low but remained within the desirable range of between 100 and about 2000. As shown in Table C2, adhesion values ranged from 134 (+/-33) to 154 (+/- 14.5) g/cm.

Shear values were measured by cutting three strips of the prepared laminates 2.5 cm wide and 7.5 cm in length. A 3.5 cm wide by 5.0 cm long strip of Mylar, a polyester film available from DuPont de Nemours, E.I Co., Wilmington Delaware also owner of the trademark "Mylar", is applied to the adhesive strip so as to provide an overlap of 2.5 cm in the lengthwise direction. These are laminated using a 2.0 kg (4.5 lb). rubber roller and allowed to equilibrate for 20 minutes. The specimen is mounted into the jaws of the Instron and pulled at a speed of 0.5 cm/min. and the peak load required to shear and separate the laminate is recorded in kg.

Desirable values range between 15-25 kg. As shown in Table C2, values ranged from 18.0 (+/- 0.8) to 23.9 (+/-0.0) kg and were within the acceptable range.

Hereinbelow, the term "pressure sensitive adhesive" may be abbreviated to "PSA".

Example A

An improved creep resistant silicone pressure sensitive adhesive containing calcium stearate was prepared as follows. Adhesive formulations with various levels (0.0, 2.5, 5.0 and 10.0 grams) of calcium stearate in a silicone pressure sensitive adhesive were prepared as follows. As shown in Table A, Adhesive I was mixed with varying amounts of calcium stearate (Table A1). The formulations were poured onto a polyester release liner (SCOTCHPAK^R 1022 Fluoropolymer coated liner, 3M Company, St. Paul, MN 55144) and the solvent was allowed to evaporate at room temperature (25°C.) for a minimum of 24 hours. The resultant compositions were evaluated for creep resistance by taking an 11 gram sample of each formulation (N=3) and placing it into wells (0.9 cm. deep, 3.8 cm. in diameter) in a test apparatus consisting of a series of wells at the top of an aluminum block measuring 457 mm (18 inches) wide, 356 mm (14 inches) tall and 25.4 mm (1 inch) thick. The adhesive was formed to fit into individual test wells and the entire test apparatus was placed in a 125°C. oven in a horizontal position for 15 min. to soften the adhesive. The test apparatus was removed and the individual pieces of the adhesive were pressed flat to form disks measuring about 0.9 cm. X 3.8 cm. and pressed onto an aluminum plate and then placed in a vertical position in the oven maintained at 125°C. The distance the adhesive flowed down the vertical

surface of the aluminum plate was measured periodically to determine flow or creep.

The effectiveness of calcium stearate in reducing flow and imparting creep resistance of the silicone adhesive is shown in Table A2. Calcium stearate provided reinforcement of the silicone adhesive, reduced flow and imparted creep resistance proportional to its loading level in the adhesive. The results on Table A2 show that adding calcium stearate was effective over the range of <5 wt% to 20 wt% with the preferred range being between 1 to 10 wt%. Standard deviations are based on 3 replicates of each sample (signified by N = 3).

TABLE A1

ADHESIVE I CONTAINING CALCIUM STEARATE

Formulation Number	Adhesive I[a]		Calcium Stearate		
	WT%	Grams	Grams	WT% Solution	WT% Tape
1	100	100	0	0	0
2	95	95	2.5	2.6	5
3	90	90	5.0	5.3	10
4	80	80	10.0	11.1	20

[a] Adhesive I is a 50 wt% solution of a high silanol containing adhesive in hexane solvent.

TABLE A2

EFFECT OF CALCIUM STEARATE ON FLOW OF ADHESIVE I

Formulation Number	Calcium Stearate WT%	Flow in (inches)[a] mm — Time In Minutes — Mean +/- SD, N=3[b]: 15	30	45	60	Maximum flow after 60 min.
1	0	30.5 +/- 1.5 (1.20 +/- 0.06)	53.3 +/- 2.5 (2.10 +/- 0.10)	74.4 +/- 3.8 (2.93 +/- 0.15)	94.0 +/- 2.5 (3.70 +/- 0.10)	94.0 +/- 2.5 (3.70 +/- 0.10)
2	5	2.5 +/- 0.00 (0.10 +/- 0.00)	7.6 +/- 0.00 (0.30 +/- 0.00)	14.5 +/- 0.8 (0.57 +/- 0.03)	26.7 +/- 1.3 (1.05 +/- 0.05)	26.7 +/- 1.3 (1.05 +/- 0.05)
3	10	1.8 +/- 0.8 (0.07 +/- 0.03)	5.6 +/- 0.8 (0.22 +/- 0.03)	9.7 +/- 0.8 (0.38 +/- 0.03)	16.5 +/- 1.3 (0.65 +/- 0.05)	16.5 +/- 1.3 (0.65 +/- 0.05)
4	20	1.3 +/- 0.00 (0.05 +/- 0.00)	3.3 +/- 0.8 (0.13 +/- 0.03)	5.1 +/- 0.00 (0.20 +/- 0.00)	6.4 +/- 0.00 (0.25 +/- 0.00)	6.4 +/- 0.00 (0.25 +/- 0.00)

a Flow was evaluated by placing an 11 gram sample of adhesive, 3.8 cm. diameter and 0.9 cm. thick, onto a vertical aluminum surface in an oven maintained at 125°C.

b N=Number of replicates for each formulation, upon which standard deviation is based.

Example B

An improved creep resistant amine-compatible, low silanol containing silicone adhesive by co-formulating with a non-amine compatible high silanol silicone adhesive was prepared as follows:

An adhesive formulation consisting of a low silanol containing amine-compatible silicone adhesive, Adhesive II and a high silanol containing silicone adhesive, Adhesive I, was prepared as shown in Table B1. The adhesive solutions were blended to homogeneity and poured onto a polyester release liner (SCOTCH-PAK[R] 1022 Fluoropolymer Coated Liner, 3M company, St. Paul, MN 55144). The solvent was allowed to

evaporate at room temperature (25 • C.) for a minimum of 24 hours before testing.

These compositions were evaluated for flow reduction and creep resistance by the same method as outlined in Example A.

Adhesive II has lower cohesive strength and exhibits significantly more flow when compared to Adhesive I. In many cases this is a disadvantage where an amine-compatible adhesive is required. By combining Adhesive I with Adhesive II, a significant reduction of flow and improved creep resistance was achieved. This is significant since reinforcing excipients such as calcium stearate are not effective in reducing flow of Adhesive II, the low silanol containing, amine-compatible Adhesive.

TABLE B1

BIO-PSA SILICONE ADHESIVES

Formulation Number	Adhesive I[a]		Adhesive II[b]	
	WT%	Grams	WT%	Grams
1	100	100	0	0
2	0	0	100	100
3	50	50	50	50

a Adhesive I is a 50 wt% solution of a high silanol containing adhesive in hexane solvent.

b Adhesive II is a 50 wt% solution of a low silanol containing amine-compatible adhesive in hexane solvent.

TABLE B2

EFFECT OF ADHESIVE I ON COLD FLOW OF ADHESIVE II

Formulation Number	Adhesive	Flow in (inches)[a] mm Time In Minutes Mean +/- SD, N=3[b] 15	30	45	60	Maximum flow after 60 min.
1	I	1.5 +/- 2.5 (0.06 +/- 0.10)	35.6 +/- 5.1 (1.40 +/- 0.20)	58.4 +/- 5.1 (2.30 +/- 0.20)	71.1 +/- 5.1 (2.80 +/- 0.20)	71.1 +/- 5.1 (2.80 +/- 0.20)
2	II	68.6 +/- 5.1 (2.70 +/- 0.20)	119.4 +/- 5.1 (4.70 +/- 0.20)	165.1 +/- 7.6 (6.50 +/- 0.30)	198.1 +/- 2.5 (7.80 +/- 0.10)	198.1 +/- 2.5 (7.80 +/- 0.10)
3	I & II (1:1)	38.1 +/- 2.5 (1.50 +/- 0.10)	58.4 +/- 2.5 (2.30 +/- 0.10)	81.3 +/- 5.1 (3.20 +/- 0.20)	106.7 +/- 5.1 (4.20 +/- 0.20)	106.7 +/- 5.1 (4.20 +/- 0.20)

a Flow was evaluated by placing an 11 gram sample of adhesive, 3.8 cm. diameter and 0.9 cm. thick, onto a vertical aluminum surface in an oven maintained at 125°C.

b N=Number of replicates for each sample, upon which standard deviation is based.

Example C

The stability of improved creep resistant silicone pressure sensitive adhesive containing calcium stearate was defined as follows:

This example details a stability and shelf-life test for similar formulations as in Example A. A formulation of a creep resistant silicone pressure sensitive adhesive was prepared by blending calcium stearate with a solution of a silicone pressure sensitive adhesive and cast to form a tape whose properties (eg. tack, peel, adhesion and shear strength) were evaluated initially and after 1 and 3 months.

Adhesive I was mixed with varying amounts of calcium stearate (0 and 5 grams) as shown on Table C1. The silicone adhesive solutions with and without calcium stearate were cast onto a polyester release liner (SCOTCHPAK^R 1022 Fluoropolymer coated Liner, 3M Company, St. Paul, MN 55144) and allowed to air dry at room temperature (25 °C.) for 30 minutes to achieve a dry film thickness of 76.2 to 101.6 µm (3 to 4 mils). The dried adhesive/release liner was then laminated on a 5 mil sheet of polyester using a 2.0 kg (4.5 lb). rubber transfer roll.

Tapes were stored at room temperature (25 °C.) and tested initially (after 2 weeks) and after 1 and 3 months to evaluate the stability of the adhesives.

Tape properties important to the performance of adhesives used in a transdermal drug delivery tape such as tack, peel, adhesion and shear strength were evaluated and were found to be very good. Results of these studies are shown in Table C2. The control adhesive possesses tack, peel, adhesion and shear strength values suitable for use as an adhesive to affix a transdermal drug delivery device to the skin. The test results show that these values were stable over the 3 month period.

Incorporation of calcium stearate into the adhesive produces a desirable slight increase in tack properties and a slight decrease in adhesion values. Although peel values generally increase slightly over time, values less than 50 g/cm are considered acceptable. The data shows values greatly below this acceptable value.

This data demonstrates that calcium stearate is compatible with a high silanol containing silicone adhesive at levels as high as 10 wt% and results in useful pressure sensitive adhesive compositions which exhibit an acceptable stability over time.

TABLE C1

ADHESIVE I CONTAINING CALCIUM STEARATE

Formulation Number	Adhesive I[a]		Calcium Stearate		
	WT%	Grams	Grams	WT% Solution	WT% Tape
1	100	100	0	0	0
2	90	90	5.0	5.3	10

[a] Adhesive I is a 50 wt% solution of a high silanol containing adhesive in hexane solvent.

TABLE C2

STABILITY OF IMPROVED CREEP RESISTANT TAPES PREPARED FROM ADHESIVE I CONTAINING CALCIUM STEARATE

Formulation Number	Excipient Wt%	Time Weeks (Months)	Tape Properties Mean +/- SD, N=3[a]			
			Tack (grams)	Peel (g/cm)	Adhesion (g/cm)	Shear (kg)
1	Control Adhesive I	2	135 +/- 18	0.80 +/- 0.11	706 +/- 348	23.8 +/- 0.1
		(1)	143 +/- 35	0.90 +/- 0.15	725 +/- 93	22.4 +/- 0.7
		(3)	126 +/- 25	5.20 +/- 1.10	718 +/- 105	17.3 +/- 3.6
2	Adhesive I+ 10 WT% Calcium Stearate	2	156 +/- 27	0.80 +/- 0.11	137 +/- 33	23.9 +/- 0.0
		(1)	144 +/- 16	0.70 +/- 0.20	134 +/- 33	21.9 +/- 0.1
		(3)	182 +/- 84	4.50 +/- 0.10	154 +/- 14.5	18.0 +/- 0.8

a N=Number of replicates for each sample, upon which standard deviation is based.

Example D

Matrix-type transdermal drug delivery patches were prepared from a creep resistant silicone pressure sensitive adhesive as follows:

Transdermal adhesive matrix-type patches were prepared containing 5 wt% 17-Beta estradiol and either 0, 4 or 8 wt% of the skin penetration enhancer propylene glycol-monolaurate (PGML) using a high silanol containing silicone adhesive (Adhesive III) without calcium stearate (control) and a high silanol containing silicone adhesive, Adhesive I with 10 wt% calcium stearate as a reinforcing filler (Table D1).

The adhesive solution was cast onto a polyester release liner (SCOTCHPAK® 1022 Fluoropolymer Coated Liner, 3M Company, St. Paul, MN 55144) and was allowed to air dry at 25 °C. resulting in a matrix 127 µm (5 mil) thick. This was then laminated onto a polyester film and die cut into 4 cm. diameter patches. Transdermal patches containing 10 wt% calcium stearate as a reinforcing filler were evaluated subjectively after 1 week for functional properties including the force required to remove the release liner, finger tack and adhesion to the ventral forearm.

Results of these subjective evaluations are shown in Table D2. The force required to remove the release liner from all patch formulations was low and acceptable. Acceptable moderate to high tack was evident and good skin adhesion was observed initially after applying the patch to the ventral forearm demonstrating the suitable functional adhesive properties of these creep resistant silicone adhesive matrix-type transdermal patches.

TABLE D1

TRANSDERMAL PATCHES CONTAINING 5 WT% ESTRADIOL AND VARIOUS LEVELS OF A SKIN ENHANCER-PROPYLENE GLYCOL MONOLAURATE (PGML)

Formulation Number	Adhesive	PGML WT%	Estradiol WT%	Calcium Stearate WT% [a]
1	III	0	5	0
2	III	4	5	0
3	III	8	5	0
4	I	0	5	10.0
5	I	4	5	10.0
6	I	8	5	10.0

[a] Where the reinforcing agent is calcium stearate (cs) formulated with Adhesive I.

TABLE D2

SUBJECTIVE MEASUREMENT OF PEEL, TACK AND SKIN ADHESIVE PROPERTIES OF TRANSDERMAL PATCHES[a] CONTAINING 5 WT% ESTRADIOL AND VARIOUS LEVELS OF SKIN ENHANCER PROPYLENE GLYCOL MONOLAURATE (PGML)

Formulation Number	PGML[b] WT%	Excipient[c] WT%	Subjective Properties[d] Peel Force	Finger Tack	Skin Adhesion
4	0	10	1	3	3
5	4	10	2	4	3
6	8	10	3	4	4

a Pressure sensitive adhesive matrix contains 5 wt% estradiol.

b Propylene glycol monolaurate (PGML).

c Calcium stearate (cs) as a reinforcing filler.

d Subjective adhesive properties:

0 = none

1 = very slight

2 = slight

3 = moderate

4 = high

Example E

Creep resistance of matrix-type transdermal drug delivery patches was determined as follows:

The viscoelastic properties of the transdermal drug delivery matrix-type patches prepared in Example D were evaluated on a dynamic spectrometer (Rheometrics Dynamic spectrometer, Model RMS 800, Rheometrics Inc., Piscataway, NJ 08854). The adhesive matrix from patches was transferred to 25 mm. diameter parallel plates and built up to a thickness of 1.0 mm. Properties of adhesive composition were characterized between an angular frequency sweep of from 0.1 to 100 rad/sec and 30 °C. at less or equal to 10 percent strain.

The following viscoelastic parameters were evaluated as a function of frequency:

1. Elastic Storage Modulus (G', dyne/cm^2) (N/m^2)

2. Dynamic Viscosity (Poise) (Pa•s)

The viscoelastic properties of the transdermal adhesive matrix with and without calcium stearate characterized at a sweep frequency of 0.1 rad/sec or 100 rad/sec are shown in Tables E1 and E2, respectively.

Formulation of skin penetration enhancers such as propylene glycol monolaurate (PGML) into the silicone adhesive has a plasticizing effect on the adhesive and increases flow properties. As the weight percent loading of the skin penetration enhancer (PGML) is increased in the silicone adhesive matrix, the storage modulus (G'), loss modulus (G") and, dynamic viscosity decreased while the loss tangent (TAN-DELTA, G"/G') increased.

Formulation of 10 wt% calcium stearate in the matrix containing 5 wt% 17-Beta Estradiol resulted in improved creep resistance as reflected by a higher storage modulus (G'), loss modulus (G") and dynamic viscosity and lower loss tangent (TAN-DELTA, G"/G') compared to the same drug containing adhesive matrix without calcium stearate.

Formulation of 10 wt% calcium stearate in the adhesive matrix containing drug and skin penetration enhancer counteracted the plasticizing effect of PGML and resulted in an improvement in the viscoelastic properties of the silicone adhesive matrix (e.g. 4 wt% PGML) at both low and high strain rates (e.g. 0.1 rad/sec. as shown in Table E1 and 100 rad/sec. in Table E2).

TABLE E1

VISCOELASTIC PROFILE OF A TRANSDERMAL DRUG DELIVERY SILICONE PRESSURE SENSITIVE ADHESIVE MATRIX AT A FREQUENCY OF 0.1 RAD/SEC

Formulation Number	Adhesive	PGML[a] WT%	Calcium[b] Stearate	Viscoelastic Properties: Storage Modulus (DYNE/CM^2 X 10^{-5}) N/m^2 x 10^{-5}	Loss Modulus (DYNE/CM^2 x 10^{-6}) N/m^2 x 10^{-6}	Dynamic Viscosity (Poise) x 10^{-7} Pa·s	Loss Tangent
1	III	0	0	(9.95) 0.995	(1.350) 0.135	(1.680) 0.168	1.36
2	III	4	0	(0.45) 0.045	(0.080) 0.008	(0.090) 0.009	1.76
3	III	8	0	(0.17) 0.017	(0.030) 0.003	(0.040) 0.004	1.76
4	I	0	10	(32.10) 3.21	(2.740) 0.274	(4.220) 0.422	0.85
5	I	4	10	(1.83) 0.183	(0.290) 0.029	(0.340) 0.034	1.58
6	I	8	10	(0.26) 0.026	(0.040) 0.004	(0.050) 0.005	1.70

a Propylene glycol monolaurate (PGML), a skin penetration enhancer.

b Pressure sensitive adhesive matrix contains 5 wt% estradiol and 0 or 10 wt% calcium stearate as a reinforcing filler (cs) in a high silanol containing silicone psa.

TABLE E2

VISCOELASTIC PROFILE OF A TRANSDERMAL DRUG DELIVERY SILICONE PRESSURE SENSITIVE ADHESIVE MATRIX AT A FREQUENCY OF 100 RAD/SEC

				Viscoelastic Properties			
Formulation Number	Adhesive	PGML[a] WT%	Calcium[b] Stearate	Storage Modulus (DYNE/CM^2) x 10^{-5} N/m^2	Loss Modulus (DYNE/CM^2) x 10^{-6} N/m^2	Dynamic Viscosity (Poise) x 10^{-7} Pa·s	Loss Tangent
1	III	0	0	(1.00) 0.100	(2.42) 0.242	(1.03) 0.103	0.24
2	III	4	0	(0.42) 0.042	(2.52) 0.252	(0.49) 0.049	0.59
3	III	8	0	(0.11) 0.011	(1.07) 0.107	(0.15) 0.015	0.98
4	I	0	10	(1.16) 0.116	(2.43) 0.243	(1.18) 0.118	0.21
5	I	4	10	(0.69) 0.069	(2.85) 0.285	(0.74) 0.074	0.41
6	I	8	10	(0.16) 0.016	(1.42) 0.142	(0.21) 0.021	0.89

a Propylene glycol monolaurate (PGML), a skin penetration enhancer.

b Pressure sensitive adhesive matrix contains 5 wt% estradiol and 0 or 10 wt% calcium stearate as a reinforcing filler (cs) in a high silanol containing silicone psa.

Example F

Improved creep resistant silicone pressure sensitive adhesive containing reinforcing excipients were prepared as follows:

Various levels of polyacrylic acid sold under the trademark Carbopol 934P, owned by B.F. Goodrich Chemical Group, Cleveland, Ohio, ethyl cellulose sold under the trademark Ethocel, Type 46080, owned by Dow Chemical, Midland, Michigan and magnesium stearate sold under the trademark Hy-Qual NF Impalpable Powder, owned by Mallinckrodt, Inc, Lodi, New Jersey, were formulated with Adhesive I as shown in Table F1 and processed and evaluated for creep resistance as outlined in Example A.

Although Carbopol 934P is a pharmaceutical excipient useful for its thixotropic properties and increasing viscosity of pharmaceutical formulations, it was surprisingly not effective in reducing the flow properties of the high silanol containing silicone adhesive.

Ethyl cellulose, also useful as a thickening agent with a greater hydrogen bonding potential, was very effective in reducing the flow properties of the high silanol containing silicone adhesive proportional to its loading level in the adhesive. The preferable loading level of ethyl cellulose in the silicone adhesive was found to be between about 10 and 20 wt. percent.

Surprisingly, magnesium stearate which is a pharmaceutical excipient used as a lubricant in oral dosage forms, was also found to be very effective in reducing the flow properties of the high silanol containing silicone adhesive when formulated at levels of 10 to 20 wt. percent.

TABLE F1

ADHESIVE I CONTAINING PHARMACEUTICAL EXCIPIENTS

Formulation Number	Adhesive I[a]		Excipients[b]			
	WT%	Grams	Type	Grams	WT% Solution	WT% Tape
1	100	100	-	-	-	-
2	99.5	99	ca	0.5	0.5	1
3	97.4	95	ca	2.5	2.6	5
4	94.7	90	ca	5.0	5.3	10
5	88.9	80	ca	10.0	11.1	20
6	99.5	99	ec	0.5	0.5	1
7	97.4	95	ec	2.5	2.6	5
8	94.7	90	ec	5.0	5.3	10
9	88.9	80	ec	10.0	11.1	20
10	99.5	99	ms	0.5	0.5	1
11	97.4	95	ms	2.5	2.6	5
12	94.7	90	ms	5.0	5.3	10
13	88.9	80	ms	10.0	11.1	20

[a] Adhesive I is a 50 wt% solution of a high silanol containing silicone adhesive in hexane solvent.

[b] Excipients include Carbopol 934P (ca), ethyl cellulose (ec) and magnesium stearate (ms).

TABLE F2

EFFECT OF CARBOPOL 934P ON FLOW OF ADHESIVE I

Formulation Number	WT% Carbopol 934	Flow in (inches)[a] mm, Time In Minutes, Mean +/- SD, N=3[b]: 15	30	45	60	Maximum flow after 60 min.
1	0	2.3 +/- 1.3 (0.09 +/- 0.05)	8.6 +/- 2.0 (0.34 +/- 0.08)	2.0 +/- 4.3 (0.08 +/- 0.17)	35.6 +/- 7.6 (1.40 +/- 0.30)	35.6 +/- 7.6 (1.40 +/- 0.30)
6	1	7.1 +/- 2.0 (0.28 +/- 0.08)	27.2 +/- 7.9 (1.07 +/- 0.31)	47.0 +/- 8.9 (1.85 +/- 0.35)	67.8 +/- 12.7 (2.67 +/- 0.50)	67.8 +/- 12.7 (2.67 +/- 0.50)
7	5	5.6 +/- 0.8 (0.22 +/- 0.03)	0.0 +/- 3.8 (0.00 +/- 0.15)	34.3 +/- 5.6 (1.35 +/- 0.22)	50.3 +/- 8.4 (1.98 +/- 0.33)	50.3 +/- 8.4 (1.98 +/- 0.33)
8	10	5.8 +/- 1.5 (0.23 +/- 0.06)	15.2 +/- 3.8 (0.60 +/- 0.15)	38.6 +/- 10.7 (1.52 +/- 0.42)	62.7 +/- 10.7 (2.47 +/- 0.42)	62.7 +/- 10.7 (2.47 +/- 0.42)
9	20	5.1 +/- 0.00 (0.20 +/- 0.00)	14.0 +/- 1.5 (0.55 +/- 0.06)	32.3 +/- 2.5 (1.27 +/- 0.10)	55.9 +/- 1.3 (2.20 +/- 0.05)	55.9 +/- 1.3 (2.20 +/- 0.05)

a Flow was evaluated by placing an 11 gram sample of adhesive, 3.8 cm. diameter and 0.9 cm. thick, onto a vertical aluminum surface in an oven maintained at 125°C.

b N=Number of replicates for each sample, upon which standard deviation is based.

TABLE F3

EFFECT OF ETHYL CELLULOSE ON FLOW OF ADHESIVE I

Formulation Number	WT% Ethyl Cellulose	Flow in (inches)[a] mm Time In Minutes Mean +/- SD, N=3[b] 15	30	45	60	Maximum flow after 60 min.
1	0	2.3 +/- 1.3 (0.09 +/- 0.05)	8.6 +/- 2.0 (0.34 +/- 0.08)	2.0 +/- 4.3 (0.80 +/- 0.17)	35.6 +/- 7.6 (1.40 +/- 0.30)	35.6 +/- 7.6 (1.40 +/- 0.30)
6	1	3.3 +/- 1.5 (0.13 +/- 0.06)	12.0 +/- 2.0 (0.47 +/- 0.08)	28.0 +/- 5.1 (1.10 +/- 0.20)	47.8 +/- 7.9 (1.88 +/- 0.31)	47.8 +/- 7.9 (1.88 +/- 0.31)
7	5	3.8 +/- 2.3 (0.15 +/- 0.09)	10.7 +/- 2.5 (0.42 +/- 0.10)	2.0 +/- 4.3 (0.80 +/- 0.17)	33.8 +/- 7.1 (1.33 +/- 0.28)	33.8 +/- 7.1 (1.33 +/- 0.28)
8	10	2.5 +/- 1.5 (0.10 +/- 0.06)	7.1 +/- 2.0 (0.28 +/- 0.08)	14.7 +/- 2.0 (0.58 +/- 0.08)	24.9 +/- 4.1 (0.98 +/- 0.16)	24.9 +/- 4.1 (0.98 +/- 0.16)
9	20	2.5 +/- 1.5 (0.10 +/- 0.06)	2.5 +/- 0.0 (0.10 +/- 0.00)	12.7 +/- 2.0 (0.50 +/- 0.08)	19.6 +/- 1.5 (0.77 +/- 0.06)	19.6 +/- 1.5 (0.77 +/- 0.06)

a Flow was evaluated by placing an 11 gram sample of adhesive, 3.8 cm. diameter and 0.9 cm. thick, onto a vertical aluminum surface in an oven maintained at 125°C.

b N=Number of replicates for each sample, upon which standard deviation is based.

TABLE F4

EFFECT OF MAGNESIUM STEARATE ON FLOW OF ADHESIVE I

Flow in (inches)[a] mm
Time In Minutes
Mean +/- SD, N=3[b]

Formulation Number	WT% Magnesium Stearate	15	30	45	60	Maximum flow after 60 min.
1	0	2.3 +/- 1.3 (0.09 +/- 0.05)	8.6 +/- 2.0 (0.34 +/- 0.08)	2.0 +/- 4.3 (0.80 +/- 0.17)	35.6 +/- 7.6 (1.40 +/- 0.30)	35.6 +/- 7.6 (1.40 +/- 0.30)
10	1	8.1 +/- 0.8 (0.32 +/- 0.03)	21.1 +/- 1.5 (0.83 +/- 0.06)	36.3 +/- 1.5 (1.43 +/- 0.06)	52.6 +/- 3.0 (2.07 +/- 0.12)	52.6 +/- 3.0 (2.07 +/- 0.12)
11	5	3.8 +/- 2.3 (0.15 +/- 0.09)	10.7 +/- 2.5 (0.42 +/- 0.10)	2.0 +/- 4.3 (0.80 +/- 0.17)	33.8 +/- 7.1 (1.33 +/- 0.28)	33.8 +/- 7.1 (1.33 +/- 0.28)
12	10	3.3 +/- 1.3 (0.13 +/- 0.05)	8.4 +/- 1.5 (0.33 +/- 0.06)	14.5 +/- 0.8 (0.57 +/- 0.03)	21.6 +/- 1.3 (0.85 +/- 0.05)	21.6 +/- 1.3 (0.85 +/- 0.05)
13	20	1.3 +/- 1.5 (0.05 +/- 0.06)	2.5 +/- 0.0 (0.10 +/- 0.00)	10.2 +/- 2.0 (0.40 +/- 0.08)	12.7 +/- 0.0 (0.50 +/- 0.0)	12.7 +/- 0.0 (0.50 +/- 0.05)

a Flow was evaluated by placing an 11 gram sample of adhesive, 3.8 cm. diameter and 0.9 cm. thick, onto a vertical aluminum surface in an oven maintained at 125°C.

b N=Number of replicates for each sample, upon which standard deviation is based.

Claims

1. A silicone pressure sensitive adhesive compatible with drugs, excipients, co-solvents and skin penetration enhancers, comprising (a) a silicone fluid and (b) a silicate resin; characterised in that the adhesive

further comprises (c) a cohesive strengthening agent in an amount of from 1.0 to 20 weight percent based on the total weight of the composition and which is selected from nonionic surfactants, fatty acid esters of glycerol and solid particulate materials, said solid particulate materials being selected from metallic salts of fatty acids, metallic salts of phosphoric acid, metallic salts of carbonic acid, polysaccharides, carboxypolymethylene, polyvinyl-pyrrolidone, polyvinylalcohol, amorphous precipitated silicas having a surface are of between 10 and 200 m^2/g.

2. The silicone pressure sensitive adhesive of claim 1 further comprising an organic solvent having reinforcing excipients dispersed therein, for dissolving the polydimethylsiloxane polymer and silicate resin, the organic solvent having a Hildebrand solubility parameter ranging from between 10.2 to 20.5$J^{1/2}/cm^{3/2}$ (5 to 10 $cal^{1/2}/cm^{3/2}$).

3. A matrix-type transdermal drug delivery device, comprising (a) a backing substrate; (b) a matrix containing a silicone, creep resistant, pressure sensitive adhesive as defined in claim 1 atop at least portions of said backing substrate, the adhesive matrix including compositions selected from drugs, co-solvents, enhancers, excipients and mixtures thereof where the silicone pressure sensitive adhesive is compatible with said drugs, co-solvents, enhancers and excipients; and (c) a release liner contacted on the matrix.

4. A matrix-type transdermal drug delivery device, comprising (a) a backing substrate; (b) a matrix which is a polymer atop at least portions of said backing substrate, the matrix containing compositions selected from drugs, excipients, enhancers, co-solvents and mixtures thereof, where the matrix is compatible with said compositions; (c) a silicone, creep resistant, pressure sensitive adhesive as defined in claim 1 disposed in a layer atop at least portions of the polymer matrix; and (d) a release liner attached to the silicone pressure sensitive adhesive.

5. A reservoir-type transdermal drug delivery device, comprising (a) a backing substrate; (b) a reservoir attached to at least portions of the backing substrate, said reservoir containing compositions selected from drugs, co-solvents, enhancers, excipients and mixtures thereof; (c) a silicone pressure sensitive adhesive as defined in claim 1 attached to the reservoir and to portions of the backing substrate not covered by the reservoir; and (d) a release liner attached to the silicone pressure sensitive adhesive.

Patentansprüche

1. Siliconhaftkleber, der verträglich ist mit Arzneimitteln, Arzneimittelträgerstoffen, Co-Lösungsmitteln und die Hautdurchdringung fördernden Stoffen, enthaltend (a) ein fluides Silicon und (b) ein Silikatharz; dadurch gekennzeichnet, daß der Haftkleber weiterhin enthält (c) ein die Kohäsion verstärkendes Mittel in einer Menge von 1,0 bis 20 Gewichtsprozent, bezogen auf das Gesamtgewicht der Stoffmischung, das ausgewählt ist aus nichtionischen oberflächenaktiven Stoffen, Fettsäureestern des Glycerins und festen, teilchenförmigen Materialien, wobei die festen, teilchenförmigen Materialien ausgewählt sind aus Metallsalzen von Fettsäuren, Metallsalzen der Phosphorsäure, Metallsalzen der Kohlensäure, Polysacchariden, Carboxypolymethylen, Polyvinylpyrrolidon, Polyvinylalkohol, amorphen gefällten Siliciumdioxiden mit einer Oberfläche zwischen 10 bis 200 m^2/g.

2. Silikonhaftkleber nach Anspruch 1, weiterhin enthaltend ein organisches Lösungsmittel mit darin dispergierten verstärkenden Arzneimittelträgerstoffen zum Lösen des Polydimethylsiloxanpolymerenund des Silikatharzes, wobei das organische Lösungsmittel einen Löslichkeitsparameter nach Hildebrand im Bereich von 10,2 bis 20,5 $J^{1/2}/cm^{3/2}$ (5 bis 10 $cal^{1/2}/cm^{3/2}$) hat.

3. Vorrichtung vom Matrix-Typ zur transdermalen Abgabe von Arzneimitteln, enthaltend (a) ein Trägersubstrat; (b) eine einen kriechbeständigen Siliconhaftkleber, wie in Anspruch 1 definiert, enthaltende Matrix zumindest auf Teilen des Trägersubstrats, wobei die Haftklebermatrix Stoffe einschließt, die ausgewählt sind aus Arzneimitteln, Co-Lösungsmitteln, fördernden Stoffen, Arzneimittelträgerstoffen und Gemischen dieser Stoffe, und der Siliconhaftkleber mit diesen Arzneimitteln, Co-Lösungsmitteln, fördernden Stoffen und Arzneimittelträgerstoffen verträglich ist; und (c) eine Abziehfolie im Kontakt mit der Matrix.

4. Vorrichtung vom Matrix-Typ zur transdermalen Abgabe von Arzneimitteln, enthaltend (a) ein Trägersubstrat, (b) eine Matrix, die ein Polymeres ist, zumindest auf Teilen des Trägersubstrats, wobei die Matrix

Stoffe enthält, die ausgewählt sind aus Arzneimitteln, Arzneimittelträgerstoffen, fördernden Stoffen, Co-Lösungsmitteln und Gemischen dieser Stoffe, wobei die Matrix mit diesen Stoffen verträglich ist; (c) einen kriechbeständigen Siliconhaftkleber, wie in Anspruch 1 definiert, der als Schicht zumindest auf Teilen der Polymermatrix angeordnet ist; und (d) eine Abziehfolie, die auf dem Siliconhaftkleber angebracht ist.

5. Vorrichtung vom Reservoir-Typ zur transdermalen Abgabe von Arzneimitteln, enthaltend (a) ein Trägersubstrat, (b) ein Reservoir, das zumindest auf Teilen des Trägersubstrats angebracht ist, wobei das Reservoir Stoffe enthält, die ausgewählt sind aus Arzneimitteln, Co-Lösungsmitteln, fördernden Stoffen, Arzneimittelträgerstoffen und Gemischen dieser Stoffe; (c) ein Silikonhaftkleber, wie in Anspruch 1 definiert, der auf dem Reservoir und auf Teilen der Trägerfolie, die nicht von dem Reservoir bedeckt sind, angebracht ist; und (d) eine Abziehfolie, die auf dem Siliconhaftkleber angebracht ist.

Revendications

1. Un adhésif de silicone sensible à la pression, compatible avec des médicaments, excipients, co-solvants et activateurs de pénétration cutanée, comprenant (a) un fluide de silicone et (b) une résine de silicate ; caractérisé en ce que l'adhésif comprend, de plus, (c) un agent renforçateur de cohésion en une quantité de 1,0 à 20 pour cent en poids par rapport au poids total de la composition et qui est choisi parmi les agents tensio-actifs non ioniques, les esters d'acides gras du glycérol et des matières particulaires solides, lesdites matières particulaires solides étant choisies parmi les sels métalliques d'acides gras, les sels métalliques d'acide phosphorique, les sels métalliques d'acide carbonique, les polysaccharides, le carboxypolyméthylène, la polyvinylpyrrolidone, l'alcool polyvinylique, les silices précipitées amorphes ayant une surface spécifique comprise entre 10 et 200 m^2/g.

2. L'adhésif de silicone sensible à la pression de la revendication 1, comprenant, de plus, un solvant organique dans lequel sont dispersés des excipients de renforcement, pour dissoudre le polydiméthylsiloxane et la résine de silicate, le solvant organique ayant un paramètre de solubilité Hildebrand compris entre 10,2 et 20,5 $J^{1/2}/cm^{3/2}$.

3. Un dispositif d'administration transdermique de médicament du type à matrice, comprenant (a) un substrat de soutien ; (b) une matrice contenant un adhésif de silicone sensible à la pression, résistant au fluage, tel que défini dans la revendication 1, sur au moins certaines parties dudit substrat de soutien, la matrice d'adhésif contenant des compositions choisies parmi des médicaments, des cosolvants, des activateurs, des excipients et leurs mélanges, l'adhésif de silicone sensible à la pression étant compatible avec lesdits médicaments, co-solvants, activateurs et excipients ; et (c) une couverture détachable sur la matrice au contact de celle-ci.

4. Un dispositif d'administration transdermique de médicament du type à matrice, comprenant (a) un substrat de soutien ; (b) une matrice qui est un polymère, sur au moins certaines parties dudit substrat de soutien, la matrice contenant des compositions choisies parmi des médicaments, des excipients, des activateurs, des co-solvants et leurs mélanges, la matrice étant compatible avec lesdites compositions ; (c) un adhésif de silicone sensible à la pression, résistant au fluage, tel que défini dans la revendication 1, disposé dans une couche placée sur au moins certaines parties de la matrice de polymère ; et (d) une couverture détachable attachée à l'adhésif de silicone sensible à la pression.

5. Un dispositif d'administration transdermique de médicament du type à réservoir, comprenant (a) un substrat de soutien ; (b) un réservoir attaché au moins à certaines parties du substrat de soutien, ledit réservoir contenant des compositions choisies parmi des médicaments, des cosolvants, des activateurs, des excipients et leurs mélanges ; (c) un adhésif de silicone sensible à la pression tel que défini dans la revendication 1, attaché au réservoir et à des parties du substrat de soutien non couvertes par le réservoir ; et (d) une couverture détachable attachée à l'adhésif de silicone sensible à la pression.

FIG. 1

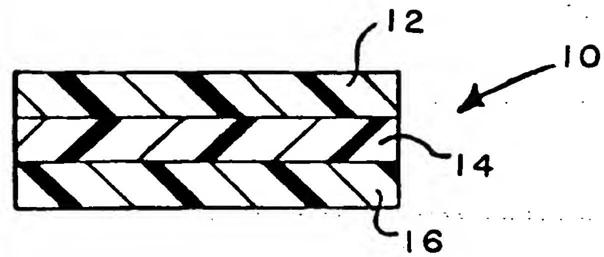


FIG. 2

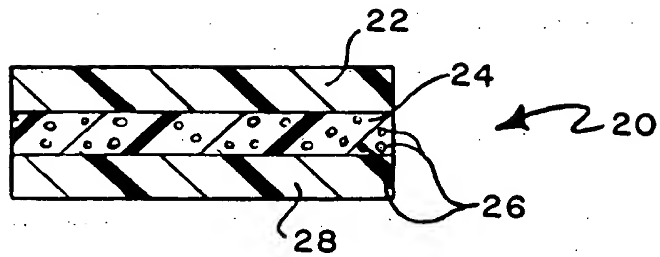


FIG. 3

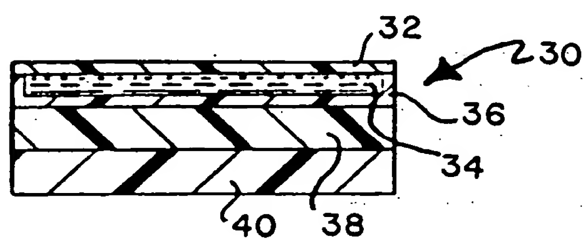
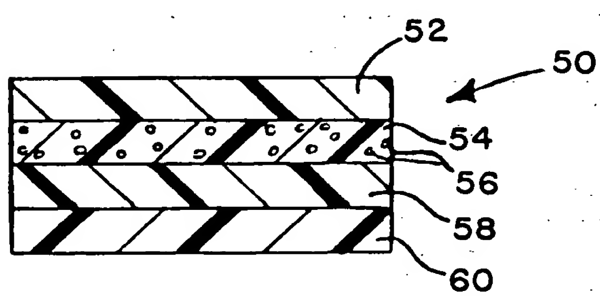


FIG. 4



US005284660A

United States Patent [19]

Lee et al.

[11] Patent Number: 5,284,660

[45] Date of Patent: * Feb. 8, 1994

[54] DELAYED ONSET TRANSDERMAL DELIVERY DEVICE

[75] Inventors: Eun Soo Lee, Redwood City; Felix Theeuwes, Los Altos; Patrick S. L. Wong, Palo Alto; Su Il Yum; Robert M. Gale, both of Los Altos; Alejandro Zaffaroni, Atherton, all of Calif.

[73] Assignee: Alza Corporation, Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Aug. 25, 2009 has been disclaimed.

[21] Appl. No.: 933,423

[22] Filed: Aug. 21, 1992

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 271,122, Nov. 14, 1988, Pat. No. 5,141,750, which is a continuation of Ser. No. 874,263, Jun. 13, 1986, abandoned.

[51] Int. Cl.^{5} A61F 13/00

[52] U.S. Cl. 424/449; 424/447; 424/448

[58] Field of Search 424/448, 449, 447

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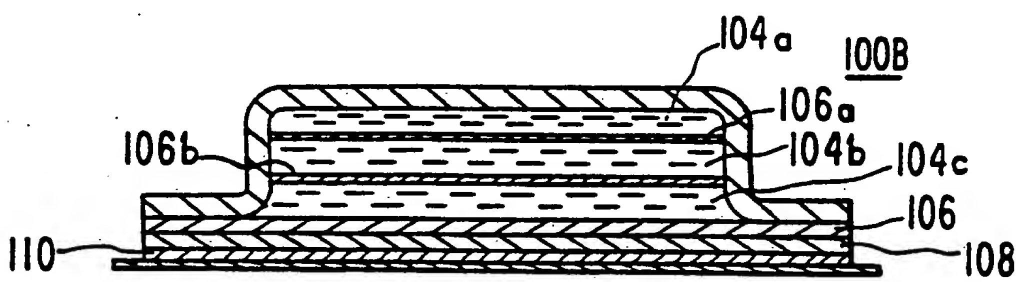
Assistant Examiner—Jyothsna Venkat
Attorney, Agent, or Firm—Jacqueline S. Larson; Jean M. Duvall; Paul L. Sabatine

[57] ABSTRACT

A diffusional drug delivery device is described which can provide for delayed onset of therapeutic effect and for delivery of the therapeutic agent in predetermined temporal patterns at optimum rates. Delay means are provided between the agent reservoir and the surface through which the agent is released by diffusion to delay the release of agent at a therapeutic rate for predetermined times after application. Suitable means include a delay membrane disposed between the releasing surface and the agent reservoir, which membrane is preferably free of undissolved agent and/or is initially impermeable to the agent and thereafter becomes permeable. One or more agent chambers defined by one or more of such membranes may be provided, whereby agents are released in predetermined temporal patterns at optimal release rates. Delayed permeability enables programmed washout periods to be obtained from the sequential and concurrent application of devices for the administration of drugs, such as nitrates, to which patients may develop a tolerance on continuous administration over extended time periods.

27 Claims, 2 Drawing Sheets



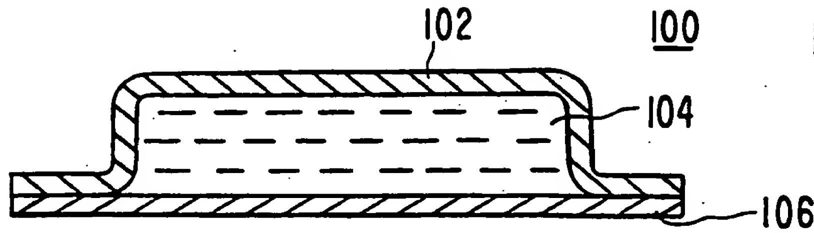


FIG. 1

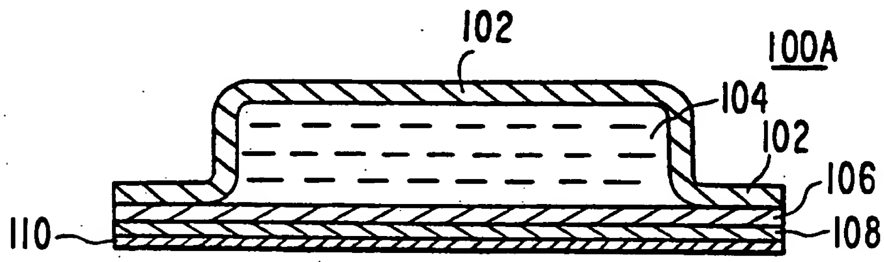


FIG. 2

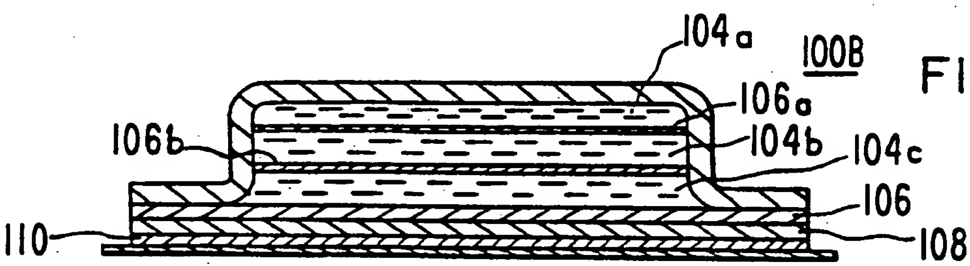


FIG. 3

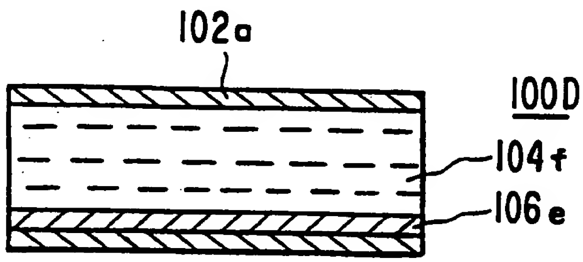


FIG. 4

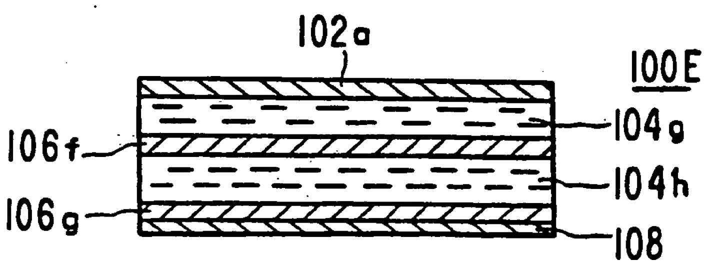


FIG. 5

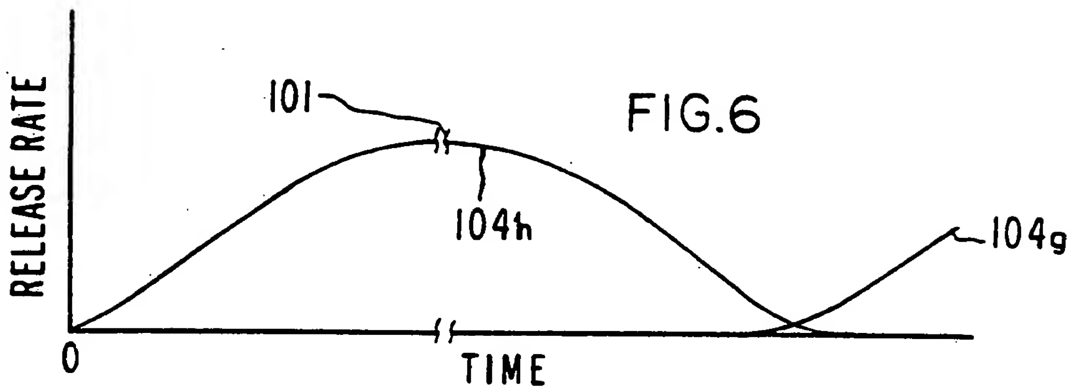


FIG.6

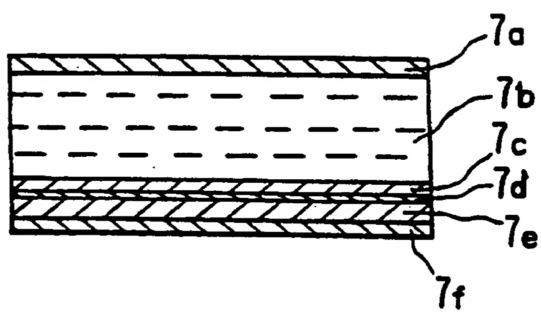


FIG.7

DELAYED ONSET TRANSDERMAL DELIVERY DEVICE

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 07/271,122, filed Nov. 14, 1988, now U.S. Pat. No. 5,141,750, which is a continuation of U.S. application Ser. No. 06/874,263, filed Jun. 13, 1986, now abandoned. This application is also related to U.S. Pat. No. 5,071,656, which is a continuation of U.S. application Ser. No. 06/874,263, referred to above. All of these applications are commonly assigned to ALZA Corporation.

FIELD OF THE INVENTION

The invention relates to diffusional drug delivery devices, and more particularly to such devices which release drugs at predetermined intervals after being placed at the site of administration.

BACKGROUND OF THE INVENTION

Illustrative examples of diffusional drug delivery devices are found in U.S. Pat. Nos. 3,598,122, 3,598,123, 3,742,951, 3,948,262, 4,031,8942 4,144,317, 4,201,211, 4,286,592, 4,314,557, 4,379,454, and 4,568,343, for example, which are incorporated herein by reference. In these devices, a drug or other active agent is released by diffusion from a reservoir through the agent-releasing surface of the device to the biological environment at which the device is applied. Such devices perform well in the administration of many agents but are not suitable for the administration of an agent whose dosage regime requires that the onset of therapeutic effect be delayed for a significant period of time after application of the device at the site of delivery. This is because the surface through which the agent is released, at the time of application, contains the agent in an amount that is significant compared to the amount in the body that gives rise to a therapeutic concentration. In those devices which utilize an agent reservoir which contains an agent at a concentration above the saturation concentration of the agent in the material from which the reservoir is formed, the agent will be present at the agent-releasing surface at the saturation concentration of the agent in the material from which the releasing surface is formed. Saturation concentration is equivalent to a thermodynamic activity of 1 (unit activity). When prior art diffusional devices are applied, agent is immediately available for diffusion into the body and the concentration of the agent at the releasing surface rapidly decreases as the concentration gradient required for steady-state diffusional delivery is established by the absorption of the agent from the releasing surface into the body. In some cases the initial rate of release is unacceptably high, and a method for reducing this initial "burst" of agent delivery is described in U.S. Pat. No. 3,923,939 to Baker et al. Even in the Baker patent, the agent-releasing surface of the diffusional embodiment contains the agent at the saturation concentration of the agent in the material in which it is dispersed, and delivery commences immediately in the manner described above.

Non-diffusional devices are known which do not immediately present drug to the biological environment when installed, such as devices which contain material in breakable microcapsules or have a fluid-imbibing pump described in commonly assigned U.S. Pat. No. 4,655,766. Diffusional delivery devices known to the prior art, however, do not possess this capability.

One of the advantages of a continuous release dosage form, such as a transdermal drug delivery device, is the improvement in patient compliance that is obtained from the concurrent removal of one device and application of a new device at the same time. This advantage is lost when removal and application occur at different times or where onset of a therapeutic effect is desired at an inconvenient time such as shortly prior to awakening. It is not possible, using concurrent application and removal of diffusional delivery devices of the prior art to substantially delay the onset of transdermal drug delivery from the time of application, such as at bedtime, until a later, often inconvenient, time, such as shortly prior to awakening. While other, non-diffusional delivery devices exist which can deliver drug after an extended delay, diffusional devices of the prior art do not possess this capability and rapidly commence delivering the drug at their intended therapeutic rates.

There is, therefore, a continuing need to provide a diffusional agent delivery device which provides for delayed onset of active agent administration and release of active agent at the desired rate at a predetermined interval after application.

SUMMARY OF THE INVENTION

The present invention provides a diffusional device for the delivery of active agents, such as drugs or other biologically active agents, in a controlled and preprogrammed manner. The devices of this invention are particularly useful in providing a predetermined, delayed onset of therapeutic effect for any desired time period after application to the skin. Thus, a device could be removed and a new one applied simultaneously, wherein the desired drug-free interval is obtained.

A diffusional delivery device, in its broadest sense, comprises an active agent reservoir from which agent passes by diffusion to the active agent-releasing surface of the device and from there into the biological environment to which it is applied. In certain embodiments of the invention, one or more delay membranes are disposed between the agent reservoir and the surface through which the agent is released from the device to produce a delayed onset of agent administration at the intended therapeutic rate. The delay membrane is substantially free of undissolved agent and may be formed from a material which in a first state has a low permeability, and in a second state has a high permeability to the agent whose release is being delayed. Typically, there will be at least a factor of two, and preferably at least an order of magnitude, difference in the permeability between the first and second states. In a presently particularly preferred embodiment, liquid triggers the change of state.

Certain embodiments of this invention possess unique characteristics by which they may be readily distinguished from other diffusional delivery devices. As discussed above, when conventional diffusional devices are placed into operation, the concentration of the agent at the agent-releasing surface decreases as the agent at the surface is absorbed by the body. According to certain embodiments of the present invention, however, the concentration of the agent at the agent-releasing surface actually increases after the device is placed into operation. This occurs because the delay membrane functions to maintain the initial concentration of the agent at the releasing surface of the device substantially

below the concentration which will exist when the device is operating at its intended steady-state agent delivery rate.

Another characteristic by which certain embodiments of this invention may be distinguished from other diffusional delivery devices has to do with the concentration or loading of active agent at the active agent-releasing surface. As noted above, it is desired, in certain embodiments, that, in its first state, the delay membrane be very impermeable to the agent being delayed. Nevertheless, it must be recognized that nothing is absolutely impermeable and even in preferred embodiments there may be small concentrations of the agent at the releasing surface. Typical delay membranes which undergo a change of state exhibit an extremely low solubility and diffusivity for the agent in their first state. As a result, even if the delay membrane has reached equilibrium with the reservoir, and may be at a thermodynamic activity of unity, the actual concentration or loading of the agent at the releasing surface will be too low to be capable of sustaining a therapeutically effective delivery rate. Thus, if the delay membrane is the agent-releasing surface of the device, the small amount of agent at the surface will be rapidly absorbed into the body at the time of application and agent will not be available until the membrane changes state and the concentration is allowed to increase as described above.

A similar condition will exist even if there is another layer, such as an adhesive, which has a high solubility for the active agent and which is disposed between the delay membrane and the body. If such a device were allowed to sit for a time sufficient to reach equilibrium (when the thermodynamic activity in the reservoir, delay membrane and adhesive are the same), then the concentration of the agent in the adhesive would be substantially higher than in the delay membrane. If, however, the thickness of the adhesive is small, the actual amount of agent available for immediate administration is likewise small. This small amount will be rapidly absorbed as described above and will not be replenished until the delay membrane changes state or otherwise passes agent at the higher, therapeutically effective rates. This condition is addressed according to this invention by, for example, keeping the adhesive layer thin, establishing a shelf life for the product which is sufficiently short with respect to the time to reach equilibrium concentration so that the concentration in the adhesive layer is kept low, or a combination thereof.

Accordingly, the agent-releasing surfaces of certain embodiments of our invention are characterized by being substantially free of agent at the time they are applied to the body. As used herein, the term "substantially free of agent" means either free of agent or containing an amount of agent insufficient to establish and maintain therapeutically effective agent delivery rates at the time of application to the delivery site.

As used herein, the term "therapeutically effective" rate or amount refers to a rate or amount of active agent that provides a therapeutic or beneficial result or effect.

As used herein, the terms "drug", "agent" and "active agent" are used interchangeably and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect.

In accordance with one embodiment of the invention, a device suitable for transdermal administration has a backing layer which is not permeable to the agent to be delivered. Agent is contained in a reservoir contiguous to the backing layer. The agent may be in solution, in combination with other components, in suspension, or in powder form. A delay membrane is disposed contiguous to the agent reservoir. In one state, the delay membrane is not permeable to the agent, whereby the agent cannot diffuse from the device. In another state, the delay membrane is permeable to the agent, and will permit diffusion of the agent at the desired rate.

In accordance with a preferred embodiment of the invention, the delay membrane is activated by moisture, such as is readily available from the site of administration such as the cutaneous surface, particularly in occluded regions. The delay membrane may alternatively be moistened by dipping into a liquid immediately prior to application. Water serves as the activating liquid where the membrane is a hydrophilic polymer. Other liquids, such as ethanol, can change the permeability of particular membranes.

Preferred delay membrane polymers are hydrophilic or semihydrophilic polymers, including polyvinyl alcohol, polyvinyl pyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose and hydroxypropylmethylcellulose. The backing layer and membrane may be heat sealed, where the membrane polymer is fabricated with integral plasticizer. Alternatively, layers are fastened with an adhesive, such as a polyisobutylene copolymer, or silicone-based adhesives.

In accordance with another embodiment of the invention, activatible delay membranes form chambers, which separate components until activated. In one embodiment, incompatible agents are prevented from interacting by a membrane barrier. Alternatively, other agents which act upon the active agent are stored within a chamber until activation, whereupon the agents are mutually exposed. In another embodiment, active agents to be released at different times are provided in separate, non-coplanar chambers.

In accordance with yet another aspect of the invention, the hydrophilic delay membrane is laminated with heat-sealable material, such as polyethylene, whereby the backing layer and laminate are heat-sealed to enclose an active agent reservoir.

In accordance with yet another embodiment of the invention, a device is installed which presents no drug to the biological environment when initially installed, and which delivers drug by diffusion after a delay.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates in cross section a delivery device of the present invention having a single agent reservoir and delay membrane.

FIG. 2 is a device as in FIG. 1, but further including a rate-controlling layer and an adhesive layer.

FIG. 3 illustrates a multi-agent device according to the invention having three delay membranes.

FIG. 4 illustrates in cross section another delivery device according to the invention.

FIG. 5 illustrates a two-agent, two-membrane, non end-sealed device according to the present invention.

FIG. 6 is a theoretical plot of the release rate vs. time for the device shown in FIG. 5.

FIG. 7 illustrates in cross section another device of the present invention, which is discussed in Example 1.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

With reference to the Figures, which are not drawn to scale, the devices shown represent, for purposes of illustration, transdermal delivery devices because these are preferred embodiments of this invention. It must be recognized, however, that this invention is applicable to delivery devices generally and in non-transdermal application certain components such as adhesives and backing layers can be omitted. A transdermal delivery device according to this invention may include an active agent-impermeable backing member, an active agent reservoir, and a delay membrane which in a first state is impermeable to the active agent and in a second state is permeable to the active agent. The delay membrane may be a glassy polymer which blocks agent diffusion to the skin and which, in the presence of moisture, swells by absorbing water, becoming permeable to the agent.

Transdermal device 100, shown in FIG. 1, includes an active agent-impermeable backing support layer 102, an active agent reservoir 104, and a delay membrane 106. When maintained in contact with a wearer's skin by an adhesive overlay or a belt, buckle or elastic band (not shown), for example, delay membrane 106 undergoes a change of state whereby the permeability of membrane 106 to the active agent and the concentration of the agent therein both start to increase.

Backing support layer 102 is not permeable to the active agent. Appropriate materials are known to the art and include, but are not limited to, metallized polyester films, polyethylene or polypropylene. Active agent reservoir 104 contains the skin-permeable drug or other active agent desired to be delivered, dissolved or dispensed in a carrier therefor. Agent reservoir 104 also may contain stabilizing agents, thickeners, permeation enhancers or other additives as are known to the art.

Delay membrane 106 is preferably substantially free of undissolved active agent and is fabricated from a material which is impermeable to the agent in a first state such as dry or cold, for example, and permeable to the agent in a corresponding second state such as wet or warm. Glassy, hydrophilic polymers which become permeable upon exposure to water are presently preferred for certain embodiments because sufficient water for causing the change of state is normally available from skin, particularly when it is occluded.

Examples of materials suitable as a delay membrane include polyvinyl alcohol (PVA), polyacrylamide, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, polyacrylic acid, polyvinyl pyrrolidone (PVP), and hydroxyethylmethacrylate (HEMA). Albumin, gelatin and cellulose may also be used. Additionally, delay membranes which are activated by non-aqueous agents may be provided. Activation is achieved by immersing the device in the liquid, such as ethanol, water or phosphate-buffered saline, or by providing isolated releasable liquid within the device. Other mechanisms by which the delay membrane can be controllably converted from an impermeable to a permeable state are within the scope of this invention.

Device 100A, shown in FIG. 2, has a rate-controlling membrane 108 disposed in combination with delay membrane 106. Rate-controlling membrane 108 may control the release rate of active agent from the device, the rate of imbibition of the activating fluid into the device, or both. If rate-controlling membrane 108 controls the release rate of agent, either delay membrane 106 or rate-controlling membrane 108 may be positioned in abutting conformity to active agent reservoir 104. If rate-controlling membrane 108 controls the rate of water imbibition into the device, and thus the time required to cause delay membrane 106 to change state, it should be positioned as shown in FIG. 2. Rate-controlling membrane 108 may be fabricated from permeable, semipermeable or microporous materials which are known to the art to control the rates of agents or fluids into and out of delivery devices.

Lamina 110 is an adhesive layer which, in accordance with one embodiment, contains a predetermined amount of drug which serves to saturate the skin for more rapid therapeutic effects where desired. Silicone compounds are commonly used as adhesives; however, numerous materials are known which possess the requisite strength and skin compatibility. An adhesive overlay or other means for maintaining the device on the skin can be employed instead of, or in combination with, adhesive lamina 110.

In FIG. 3, an alternative device 100B has a plurality of active agent reservoirs 104*a*, 104*b* and 104*c* separated by delay membranes 106*a* and 106*b*. The agents in reservoirs 104*a*, 104*b* and 104*c* may be the same or they may be different or one reservoir may contain an agent different from that in the other two reservoirs, depending upon the therapeutic regime desired. Membrane 106*a* prevents mixing of active agent in reservoirs 104*a* and 104*b*, while membrane 106*b* separates active agent in reservoirs 104*b* and 104*c*. The membranes may also have the same or different thickness depending upon the temporal delivery pattern desired and, as shown, membrane 106*b* has a greater thickness than that of membrane 106*a*. Rate-controlling membrane 108 may control the rate of water imbibition into device 100B so that activation of delay membranes 106*a* and 106*b* can be delayed substantially beyond the activation of delay membrane 106 to provide for sequential delivery of the active agents in the three agent layers.

In operation, water migrates into device 100, 100A or 100B from the skin surface or other source, typically by osmosis or diffusion, passing through intervening adhesive lamina 110, if present, rate-controlling membrane 108, if any, and then to delay membrane 106. Upon contact with the water, delay membrane 106 becomes progressively more permeable to the active agent. As the delay membrane becomes permeable, active agent in reservoir 104 or 104*c* diffuses through rate-controlling layer 108, and thence through adhesive lamina 110 to the skin surface. As water passes to delay membranes 106*b* and 106*a* at a rate established by rate-controlling membrane 108, they, in turn, become more permeable to the active agents and the agents are sequentially released from layers 104*b* and 104*a*, respectively. As the delivery rates of the agents in each of the reservoirs increase towards their steady-state rates, the concentration of that agent in adhesive layer 110 also increases. It has been demonstrated that delay membranes require a longer hydration time period as thickness is increased. Accordingly, delay membrane 106*a* will activate more rapidly than delay membrane 106*b* if the same material is used in both membranes.

FIGS. 4 and 5 illustrate laminated devices 100D and 100E, respectively, according to this invention. These devices are not end-sealed. Each of devices 100D and

100E has a backing layer 102*a*. Active agent reservoir laminae 104*f*, 104*g* and 104*h* may, in addition to permeation enhancers and stabilizing agents, contain rheological modifiers, viscosity boosters or thixotropic/gelling agents to prevent flow of the agent matrix beyond the device confines. Delay membranes 106*e*, 106*f* and 106*g* do not flow, as these membranes, generally, have a rigid, glass-like rheology when dry. When moistened, or wet, the delay membranes continue to retain integrity.

The device of FIG. 4 is suitable for delaying the onset of therapeutic effect for a period of time after application. The device of FIG. 5 illustrates a configuration which is capable of delivering two active agents sequentially or, if the same agent is contained in reservoirs 104*g* and 104*h*, capable of providing a predetermined interruption in administration coupled with a predetermined delay in therapeutic onset. By concurrently applying a fresh device and removing the exhausted device at the same time each day or every other day, for example, a complex repetitive pattern of agent administration can be obtained with a high degree of patient compliance. Thus, if nicotine were the drug delivered in the embodiments of FIGS. 4 and 5, periodic periods of no nicotine would be experienced by the patient during those times, such as during sleep, when the patient does not require the drug. In this example, the device of FIG. 4 would be a 24-hour device and the device of FIG. 5 would be a 48-hour device. The delay membranes would be selected to produce the desired "off" periods, typically considered to be in the range of from 4–12 hours.

FIG. 6 illustrates the theoretical effect produced by device 100E in which rate-controlling membrane 108 controls both the rate of water imbibition into the device and the rate of active agent release from the device. The indicated missing time interval 101 represents the substantially constant agent release rate established by membrane 108. Rate-controlling membrane 108 is also selected to control the rate of imbibition of water so that delay membrane 106*f* becomes permeable to the active agent only after the amount of agent in reservoir 104*h* has become substantially depleted. This permits the blood levels of the agent to drop in the time period running from the end of period 101 until delivery from reservoir 104*g* reaches effective rates which occurs when curve 104*g* continues to rise, in a manner similar to curve 104*h*.

Typically, the devices of this invention include a removable release liner (not shown) on the device surface to be placed on the skin or mucosa, which liner is removed prior to placement. Such release liners are known to the art and are typically of siliconized paper or siliconized polymer or the like.

The present invention is particularly useful in delivering those active agents which should not be delivered in a continuous manner over a prolonged period of time. Agents which may be beneficially delivered according to this invention include agents where a therapeutic effect is desired at an inconvenient time or where no therapeutic effect is desired for a particular time period. These agents include, but are not limited to, nicotine (for providing a period of no nicotine delivery during sleep and then providing nicotine in a therapeutic amount at or just prior to awakening); caffeine (for providing delivery of caffeine in the morning hours as a means of awakening); melatonin (for providing melatonin delivery during the desired sleep cycle, normally late at night, usually between about 11:00 p.m. and 6:00 a.m.); painkillers, steroidal anti-inflammatory drugs and non-steroidal antiinflammatory drugs for relieving early morning stiffness and pain; and the cardiovascular drugs (for providing initiation of delivery early in the morning, usually at about daybreak), examples of which cardiovascular drugs are the vasodilators (examples of which are nitroglycerin, amyl nitrate and other nitrates and nitrites), the beta blockers (examples of which are propranolol, timolol and atenolol), calcium channel blockers (examples of which are nifedipine and nicardipine), and ACE inhibitors (examples of which are captopril, enalapril and enalaprilat). Other active agents which may be usefully delivered from devices according to this invention are those agents, such as morphine, methodone, secoverine and benzotropine, which cause irritation from an initial burst when delivered by prior art devices; and those agents, such as the nitrates and alcohols, that require a "washout" period or period of no agent delivery so that the patient does not build up a tolerance to the agent.

One drug which is particularly suitable for delayed delivery according to the present invention is nicotine. Transdermal delivery devices for the immediate delivery of nicotine have been recently introduced for the treatment of smoking cessation. These devices are available for delivery over 24 hours, where the patient replaces the device once every 24 hours, and for delivery over 12 hours, where the patient may either replace the device once every 12 hours or wear a device for a 12-hour period, followed by no device for 12 hours. Each of these regimens can provide drawbacks. With delivery of nicotine continuously over 24 hours (with either the 24-hour patch or two 12-hour patches), certain side effects have been reported that are associated with delivery of nicotine during sleeping hours. These include abnormal dreams and insomnia. If a device is not worn during sleep in order to reduce or eliminate these side effects, then a new nicotine patch would not be applied until after awakening in the morning. However, when no nicotine has been delivered during the night, the plasma nicotine concentrations will be low and smokers encounter early morning withdrawal symptoms such as "morning craving" and the urge to smoke. Placement of a nicotine patch after awakening will not immediately relieve these cravings, and this could greatly decrease the efficacy of the transdermal devices for stopping the smoking habit.

A delayed delivery device of the present invention can be designed to be placed on the skin at dinner time or at bedtime, for example, and would not begin delivery of nicotine to the skin until shortly prior to awakening such as one to three hours prior to awakening, usually five to eight hours after initial placement, after which time therapeutic levels of nicotine would be delivered for about the next sixteen to nineteen hours. This initial delay of nicotine delivery could reduce or eliminate the side effects of abnormal dreams and insomnia because significant drug delivery will only occur during waking hours. At the same time, efficacy will be maintained because plasma nicotine concentrations will be achieved in sufficient time prior to awakening to overcome any morning craving and the urge to smoke.

Having thus generally described the present invention, the following specific examples of the invention are provided.

EXAMPLE 1

Transdermal delayed delivery devices for the delayed onset of delivery of nicotine according to the present invention and illustrated in FIG. 7 were prepared as follows.

A 0.05 mm high-density polyethylene (HDPE) film is extruded onto a siliconized polyester film (for protecting the film layer until final assembly) to give the rate-controlling membrane 7*c*. Sixty parts of ethylene vinyl acetate copolymer ("EVA") having 40% vinyl acetate content were blended with 40 parts of nicotine base until the components were well dispersed to give the active agent reservoir 7*b*. This reservoir layer was then extruded through a slot die at about 50° C. onto the HDPE membrane layer at about 0.125 mm thickness. Downstream from this, a MEDPAR ® film of 0.05 mm thickness was laminated to the other side of the EVA/-nicotine reservoir to give the nicotine-impermeable backing layer 7*a*, and the resulting composite film was taken up on a winding station.

In a separate operation, a polyisobutylene (PIB) film (85% 1,200,000 MW and 15% 35,000 MW) acrylate adhesive was solution-cast on a siliconized substrate (for protecting the adhesive until final assembly) to a dry thickness of 0.005 mm to give the adhesive tie layer 7*d*. Polyvinyl alcohol (PVA; 88% OH) film at 0.05 mm thickness was laminated to the adhesive layer to give the delay membrane 7*e*. A second acrylate adhesive layer was cast to a dry thickness of 0.05 mm on the other surface of the PVA delay membrane layer to give the contact adhesive layer 7*f*.

For the final assembly, the siliconized protective layers contacting the HDPE rate-controlling membrane and the adhesive tie layer were removed and the HDPE layer of the one laminate is laminated to the adhesive tie layer of the second laminate. Final delay-onset devices were then die cut and packaged for use.

EXAMPLE 2

The devices of Example 1 having a polyvinyl alcohol delay membrane were tested in vitro for nicotine release, in comparison with a prior art device (the Nicoderm ® transdermal patch). Release rates of nicotine over time through a 1.5 mil Hytrel ® membrane into an aqueous bath at 35° C. were determined, the Hytrel membrane being used because it simulates the water transport properties of human skin. For the test, the release liner was removed from each device, and each device was covered at its drug release surface with the Hytrel membrane to control water availability to the test device in all release rate tests. Each test was run over 24 hours at 35° C. The release medium was distilled water. Drug concentration was determined by UV absorption at 259 nm. When the devices were tested, the prior art devices began to release nicotine through the Hytrel membrane within a short period of time after coming into contact with the aqueous release medium, whereas the release rate of the devices of Example 1 was zero after 5 hours of contact.

It is clear from the above results that devices incorporating the delay membrane, as compared with the prior art devices, do not immediately release agent when the Hytrel membrane, which simulates the rate at which water would be available to the device from the skin to which it is intended to be applied, is exposed to the aqueous bath. This is due to the fact that the agent-releasing surfaces 7*f* of the embodiments of this invention were substantially free of agent when exposed to the skin whereas the corresponding surfaces 7*d* of the controls contain nicotine at unit thermodynamic activity. Continued delay of agent release is due to the impermeability of the delay membrane to the agent until the membrane has become hydrated.

The delay membranes are capable of in vivo operation as switches, preventing active agent release until the device is occluded and provided with sufficient moisture for activation from the skin. The controls will, in vivo, immediately present agent to the skin and commence agent delivery. Devices according to this invention, however, will all exhibit the delays shown before release at the intended steady-state rate will be achieved.

EXAMPLE 3

Transdermal delayed delivery devices for the delayed onset of delivery of melatonin according to the present invention are prepared as follows.

EVA 40 (EVA with 40% vinyl acetate) (2.7 g), glycerol monooleate (1.5 g; Myverolo ® 1899K, Eastman Chemical Products; "M-GMO") and chloroform (27.0 g) were added together in a vial. The vial was capped (Teflon ®-lined) and rotated for 4–6 hours, until the EVA 40 was dissolved. The resulting homogeneous solution was then poured onto a glass plate lined with a siliconized polyester release liner film (siliconized PET). The chloroform was evaporated off until the film was dry. Melatonin (0.35 g; Sigma Chemicals) was then dry blended into 1.98 g of the EVA 40/M-GMO dry film in a rubber mill until homogeneous. The resulting material, having a composition of 15 wt % melatonin, 30 wt % M-GMO and 55 wt % EVA 40, was melt-pressed to about 8 mil (0.2 mm) thickness between two sheets of siliconized PET release liner at 60° C. and 10,000 lbs. pressure. The resulting film was heat-laminated to an impermeable backing (Medpar ® or Scotchpak ®, for example). The drug matrix/impermeable backing laminate was then laminated, on the side opposite the impermeable backing, to an acrylic contact adhesive (2 mil; MSX 1010P, 3M) to provide a monolith with an adhesive tie layer.

In a separate operation, acrylic adhesive was solution-cast to a dry thickness of 0.05 mm on a siliconized PET release liner to give the contact adhesive layer. Polyvinyl alcohol (PVA; 88% OH) film at 0.05 mm thickness was laminated to the adhesive layer to give the delay membrane.

For the final assembly, the siliconized protective layer contacting the EVA/melatonin reservoir is removed and the exposed adhesive tie layer is adhered to the PVA layer of the second laminate. Discs of 19 CM^2 size each are punched or die-cut from the laminate to give final devices having 55.6 mg of melatonin per device or 2.92 mg of melatonin per CM^2.

Following the above procedures, melatonin devices identical to the above are manufactured, except that the delay membrane is formed from polyvinyl pyrrolidone. In like manner, melatonin devices are made having hydroxyethylcellulose delay membranes, having hydroxypropylcellulose delay membranes, and having hydroxypropylmethylcellulose delay membranes.

Devices according to FIGS. 1, 2, 3, 4, 5, and 7 may be produced by conventional pouching, laminating or extruding techniques as known to the art. In accordance with the invention, many configurations are constructable, wherein a wide variety of release-rate and delay

characteristics are obtainable. Additionally, different active agents, or different concentrations of the same active agent, are released at predetermined time intervals, whereby highly therapeutic results are obtained with a minimum amount of agent. Moreover, complicated dosage patterns may be administered without dependence on patient compliance and without interruption in the patient's lifestyle.

In accordance with the above described embodiments, it can additionally be seen how the invention provides for a powerful and flexible means of programming, or coordinating, the diffusional release of one or more agents from a single device, in a single application. Physicians can prescribe a complex agent administration program with far greater assurance that the regime will be adhered to. The patient need not interrupt his/her daily routine to take medication, nor can the patient forget or become confused, with respect to the timing and types of medication which must be taken. Moreover, the amount of active agent can be reduced, since therapeutic regimen can be defined more closely with delay membranes, either alone or in combination with conventional rate-controlling membranes. By providing for agent washout, particularly with agents such as nitrates to which patients may develop a tolerance, agent efficacy is enhanced while patient compliance is maintained. Additionally, agents which have limited biological half-lives may be used in lower quantities, now that a means of repeatedly and sequentially reintroducing predetermined amounts of agent has been provided by the invention.

While this invention has been described with respect to certain specific embodiments thereof, it should not be construed as being limited thereto. Numerous modifications and substitutions will suggest themselves to workers skilled in the art and may be made without departing from the scope of this invention, which is limited only by the following claims.

What is claimed is:

1. A controlled release dispensing device for delivering a drug to skin or mucosa and adapted to delay the onset of drug delivery at a therapeutically effective rate for a predetermined time after placement of said device in drug-transferring relationship to the skin or mucosa, said device comprising, in combination:

- a drug-containing reservoir having a surface through which said drug is released to the skin or mucosa, said drug being selected form the group consisting of nicotine and melatonin; and
- a drug release delay membrane comprised of hydrophilic or semihydrophilic polymer disposed between the skin or mucosa and the releasing surface of said reservoir, said delay membrane being substantially free of undissolved drug and being impermeable to said drug in a dry state and permeable thereto in a hydrated state;
- whereby said drug must pass through said delay membrane to reach the skin or mucosa and whereby release of said drug from said reservoir to the skin or mucosa at said therapeutically effective rate is delayed until the delay membrane is converted from its dry state to its hydrated state.

2. A device according to claim 1 wherein said delay membrane is converted from its dry state to its hydrated state by cutaneous liquids.

3. A delivery device for the percutaneous administration of a drug selected from the group consisting of nicotine and melatonin and adapted to delay the onset of drug delivery at a therapeutically effective rate for a predetermined time after placement of said device in drug-transmitting relationship to the skin or mucosa, said delivery device comprising;

- a backing layer impermeable to said drug;
- a drug-containing reservoir disposed between said backing layer and the skin or mucosa;
- a drug release delay membrane comprised of a hydrophilic or semihydrophilic polymer disposed between said reservoir and the skin or mucosa such that said drug must pass through said delay membrane to reach the skin or mucosa, said delay membrane being substantially free of undissolved drug and being impermeable to said drug when in a dry state and permeable to said drug when in a hydrated state; and
- means for maintaining said device in drug-transmitting relationship to the skin or mucosa.

4. A device according to claim 3 wherein said delay membrane is converted from its dry state to its hydrated state by cutaneous liquids.

5. A device according to claim 3 which further comprises a second drug-containing reservoir disposed between said backing layer and the skin or mucosa and a second drug release delay membrane comprised of a hydrophilic or semihydrophilic polymer disposed between said second reservoir and the skin or mucosa.

6. A device according to claim 3 which further comprises a rate-controlling membrane for controlling the rate at which said delay membrane becomes hydrated when the device is placed in contact with the skin or mucosa.

7. A device according to claim 3 which further comprises a rate-controlling membrane for controlling the rate at which said drug is transmitted from said drug reservoir to the skin or mucosa.

8. A device according to claim 5 which further comprises at least one rate-controlling membrane.

9. A device according to claim 3 wherein said means for maintaining said device to the skin or mucosa comprises a contact adhesive disposed between said delay membrane and the skin or mucosa.

10. A device according to claim 9 wherein the total loading of drug in said contact adhesive at the time of application to the skin or mucosa is insufficient to establish and maintain drug delivery at a therapeutic rate.

11. A device according to claim 3 which further comprises an adhesive tie layer interposed between said delay membrane and said reservoir.

12. A device according to claim 3 wherein said delay membrane is polyvinyl alcohol.

13. A device according to claim 3 wherein said drug is nicotine.

14. A method for delaying delivery of a drug selected form the group consisting of nicotine and melatonin to the skin or mucosa, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa, said device comprising;
   - a backing layer impermeable to said drug;
   - a drug-containing reservoir disposed between said backing layer and the skin or mucosa;
   - a drug release delay membrane comprised of a hydrophilic or semihydrophilic polymer disposed between said reservoir and the skin or mucosa such that said drug must pass through said delay membrane to reach the skin or mucosa, said delay membrane being substantially free of undissolved drug and being impermeable

to said drug when in a dry state and permeable to said drug when in a hydrated state; and

means for maintaining said device in drug-transmitting relationship to the skin or mucosa; and

2) changing said delay membrane of said delivery device from said dry state to said hydrated state, whereby the passage of said drug from said reservoir to the skin or mucosa is delayed.

15. The method according to claim 14 wherein said delay membrane is changed from its dry state to its hydrated state after placement on the skin or mucosa.

16. The method according to claim 14 wherein said delay membrane is changed from its dry state to its hydrated state by cutaneous liquids.

17. The method according to claim 14 wherein said delivery device further comprises a rate-controlling membrane.

18. The method according to claim 14 wherein said delay membrane is polyvinyl alcohol.

19. The method according to claim 14 wherein said drug is nicotine.

20. A method for reducing the side effects associated with the transdermal delivery of nicotine during sleeping hours, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa prior to bedtime, said device comprising:

a backing layer impermeable to nicotine;

a nicotine-containing reservoir disposed between said backing layer and the skin or mucosa;

a nicotine release delay membrane comprising polyvinyl alcohol disposed between said reservoir and the skin or mucosa such that nicotine must pass through said delay membrane to reach the skin or mucosa, said delay membrane being substantially free of undissolved nicotine and being impermeable to nicotine when in a dry state and permeable to nicotine when in a hydrated state; and

means for maintaining said device in nicotine-transmitting relationship to the skin or mucosa; and

2) changing said delay membrane of said delivery device from said dry state to said hydrated state, whereby the passage of nicotine from said reservoir to the skin or mucosa is delayed until shortly prior to awakening.

21. The method according to claim 20 wherein said delay membrane is changed from its dry state to its hydrated state after placement on the skin or mucosa.

22. The method according to claim 20 wherein said delay membrane is changed from its dry state to its hydrated state by cutaneous liquids.

23. The method according to claim 20 wherein said delivery device further comprises a rate-controlling membrane.

24. A method for relieving the early morning withdrawal symptoms associated with low plasma concentrations of nicotine during sleeping hours, said method comprising the steps of:

1) placing a delivery device onto the skin or mucosa prior to bedtime, said device comprising:

a backing layer impermeable to nicotine;

a nicotine-containing reservoir disposed between said backing layer and the skin or mucosa;

a nicotine release delay membrane comprising polyvinyl alcohol disposed between said reservoir and the skin or mucosa such that nicotine must pass through said delay membrane to reach the skin, said delay membrane being substantially free of undissolved nicotine and being impermeable to nicotine when in a dry state and permeable to nicotine when in a hydrated state; and

means for maintaining said device in nicotine-transmitting relationship to the skin or mucosa; and

2) changing said delay membrane of said delivery device from said dry state to said hydrated state, whereby the passage of nicotine from said reservoir to the skin or mucosa is delayed until shortly prior to awakening, whereby therapeutic plasma levels of nicotine are present at the time of awakening.

25. The method according to claim 24 wherein said delay membrane is changed from its dry state to its hydrated state after placement on the skin or mucosa.

26. The method according to claim 24 wherein said delay membrane is changed from its dry state to its hydrated state by cutaneous liquids.

27. The method according to claim 24 wherein said delivery device further comprises a rate-controlling membrane.

* * * * *

Annex 3

National Starch & Chemical
A member of the ICI Group

National Starch and Chemical Company
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Bridgewater, New Jersey 08807-0500
908-685-5000

DURO-TAK® 80-1057
Family of Products

Description
The DURO-TAK®1057 products are a family of high peel acrylic solution pressure sensitive adhesives designed for high performance clear film applications.

Family Members
80-1057, 80-1093, 80-1106, 80-1197

Typical Applications
- Clear film labels, decals and overlays
- Metal and film nameplates
- Transfer films and two-side coated mounting tapes
- Note: this product has not been assessed for medical applications.

Typical Performance* (1 dry mil)

	~~Polyester (2 mil)~~
180° Peel (oz/in)	
20 minutes	60
24 hours	75
1 week	100
Shear (hours)	
4 psi @ 72°F	>24
Tack (oz/sq in)	30

* Not to be used for setting specifications

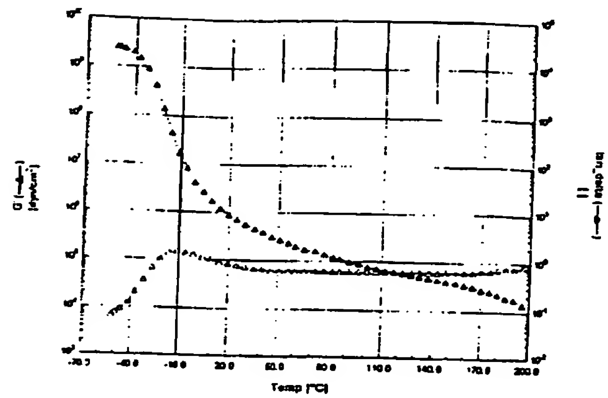
FDA Status
The dry film components of DURO-TAK®1057 products comply with the compositional requirements of the FDA Indirect Food Additive Regulation, 21 CFR 175.105 "Adhesives", 21 CFR 176.180** "Components of paper and paperboard in contact with dry food", and 21 CFR 176.170** (paragraph b) "Components of paper and paperboard in contact with aqueous or fatty food".

** subject to the extractive limitations of the regulation.

Features
- Self-crosslinking
- High peel and tack
- Excellent clarity; non-yellowing on prolonged exposure to ultraviolet light

Benefits
- One part system
- Excellent adhesion to a variety of substrates
- Suitable for a broad variety of clear film facestocks

122000



Typical Physical Properties*

- Appearance:
  - Solution: Clear, colorless to slightly yellow
  - Dry Film: Clear, colorless
- Shelf Life: 6 months in unopened containers

Product Number	Solids (%)	Viscosity (cps)	Density (lbs/gal)	Williams Plasticity (mm)	Flash Pt. (°F)	Solvent System (by weight)
80-1057	41	1000	7.2	2.75	<20	40% Isopropanol/36% Heptane/ 12% Ethyl Acetate/8% Xylene/ 4% Toluene
80-1093	53	7000	7.2	2.50	<20	62% Heptane/22% Ethyl Acetate/ 15% Toluene/1% Isopropanol
80-1106	49	3750	7.1	2.50	<20	44% Heptane/38%Ethyl Acetate/ 13%Toluene/3%Vinyl Acetate/1% Isopropanol
80-1197	46	1500	7.0	2.50	<20	43% Isopropanol/ 36% Heptane/ 16% Ethyl Acetate/5% Toluene

* Not to be used for setting specifications

Application Guide

Apply by any conventional method including reverse roll and knife-over-roll. DURO-TAK® 1057 adhesives are designed to be ready for use. If dilution is required, however, ethyl acetate (urethane grade) is suggested.

Typical adhesive deposition is 1 to 2 mils dry for most applications. Drying in a zoned oven is recommended with the last zone as hot as possible to maximize cure rate.

Storage and Handling

The DURO-TAK®1057 product family is stable for a minimum of 6 months under normal conditions. Store drums in dry areas and keep them tightly covered to prevent solvent loss and contamination.

Rotate stock using the oldest material first. Mix the adhesive thoroughly before use and do not mix it with any other products. Consult the Material Safety Data Sheet (MSDS) for hazardous ingredients, flammability, disposal, and related handling information.

Precautions

Review the MSDS carefully before use. DURO-TAK®1057 products contain flammable solvents; eliminate all sources of ignition before use. Use with adequate ventilation; avoid breathing of vapor; minimize skin contact. Migratory materials in some face stocks and end use substrates, e.g., vinyl films and foams, may affect performance. It is recommended that DURO-TAK®1057 products be thoroughly tested for a particular application before large scale use is attempted.

National Starch and Chemical Company

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P.O. Box 6500
Bridgewater, New Jersey 08807-0500
908-685-5468

PRESSURE SENSITIVE & LAMINATING ADHESIVES

DURO-TAK® 87-2196

Description: Duro-Tak 87-2196 is a moderate molecular weight, self-crosslinking, acrylic copolymer pressure sensitive adhesive supplied in an organic solvent solution.

Typical Application: Transdermal drug delivery systems

Typical Physical Properties*:

Appearance:		Solution is clear, colorless to slightly yellow Dry film is clear, colorless	
Total Solids		45	%
Brookfield Viscosity (72°F, 20 rpm, #4)		3000	cps
Solvent System:	Isopropanol	45	% by weight
	Heptane	34	
	Ethylacetate	15	
	Toluene	6	
	2,4-Pentanedione	1	
Density		7.3	lbs/gal
Solubility Parameters (Calculated by group contribution method)	Polymer	16	$J^{1/2}/cm^{3/2}$
	Solvent system	20	
Tg (Theoretical glass transition temperature)		-50	°C
Water Vapor Transmission		320	$g/m^2/24$ hours

Typical Performance Properties*:

180° Peel Adhesion:	20 minutes bond time	55	oz/in width
	24 hours bond time	64	
	1 week bond time	75	
Shear (Holding power: 8 psi @ 72°F)		15	hours
Tack (Loop)		30	oz/in^2

Test strips: 1-mil of dry adhesive backed by a 2-mil polyester film
Test panels: stainless steel

* *All numerical values given are intended for use as guidelines only and do not reflect product specifications.*

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PRESSURE SENSITIVE & LAMINATING ADHESIVES

DURO-TAK® 87-2194

Description: Duro-Tak 87-2194 is a moderate molecular weight, self-crosslinking, acrylic copolymer pressure sensitive adhesive supplied in an organic solvent solution.

Typical Application: Transdermal drug delivery systems

Typical Physical Properties*:

Appearance:	Solution is clear, colorless to slightly yellow Dry film is clear, colorless		
Total Solids		45	%
Brookfield Viscosity (72°F, 20 rpm, #4)		3000	cps
Solvent System:	Heptane	46	% by weight
	Xylene	21	
	Ethylacetate	15	
	Isopropanol	10	
	Toluene	7	
	2,4-Pentanedione	2	
Density		7.6	lbs/gal
Solubility Parameters (Calculated by group contribution method)	Polymer	16	$J^{1/2}/cm^{3/2}$
	Solvent system	17	
Tg (Theoretical glass transition temperature)		-50	°C
Water Vapor Transmission		270	$g/m^2/24$ hours

Typical Performance Properties*:

180° Peel Adhesion:	20 minutes bond time	55	oz/in width
	24 hours bond time	64	
	1 week bond time	75	
Shear (Holding power: 8 psi @ 72°F)		15	hours
Tack (Loop)		17	oz/in^2

Test strips: 1-mil of dry adhesive backed by a 2-mil polyester film
Test panels: stainless steel

* *All numerical values given are intended for use as guidelines only and do not reflect product specifications.*

FDA Drug Master File Status

Detailed information on this product is contained in FDA DMF #4571. The FDA will review this information for you upon receipt of an authorization letter from National. Please contact your technical service representative.

FDA Food Contact Status

The dry film components of Duro-Tak 87-2194 comply with the compositional requirements of the FDA Indirect Food Additive Regulation, 21 CFR 175.105 "Adhesives", 21 CFR 176.180* "Components of paper and paperboard in contact with dry food", and 21 CFR 176.170* (paragraph b) "Components of paper and paperboard in contact with aqueous or fatty food".

*subject to the extractive limitations of the regulation.

Safety Testing

As an indication of the suitability of these products for skin-contact use, National provides results from the following safety testing:

- Cytotoxicity, USP MEM Elution
- USP Biological Class VI (Plastics)
- Primary Dermal Irritancy in Rabbits
- Buehler Sensitization.

The primary dermal irritation score on Duro-Tak 87-2194 is 0.17 which is classified as "minimally-irritating". Please contact your technical service representative for more information.

Drug/Enhancer Compatibility

Compatibility with your formulating ingredients is a function of both the chemical composition and viscoelastic properties of the polymer. Please contact your technical service representative to discuss your particular application.

Product Consistency

Duro-Tak 87-2194 is produced using a computer-controlled manufacturing process in an ISO-9002 certified facility (certified by Underwriters Laboratories Inc., file no. A2910, vol. 1 issued 19-July-1994).

Application Guide

Apply by any conventional method including reverse roll and knife-over-roll. Duro-Tak 87-2194 is designed to be ready for use. If dilution is required, however, ethyl acetate (urethane grade) is suggested.

Typical adhesive deposition is 1 to 2 mils dry for most applications. Drying in a zoned oven is recommended with the last zone as hot as possible to maximize the rate of cure. Cure is dependent upon drying conditions (heat, dwell time).

Storage and Handling

Duro-Tak 87-2194 is stable for a minimum of 12 months from date of manufacture in unopened containers under normal conditions. Between 12 and 24 months from date of manufacture, the material may still be suitable for use if the integrity of the container is intact and the solids and viscosity are within specification. Store drums in dry areas and keep them tightly covered to prevent solvent loss and contamination.

Rotate stock using the oldest material first. Mix the adhesive thoroughly before use and do not mix it with any other products. Consult the Material Safety Data Sheet (MSDS) for hazardous ingredients, flammability, disposal, and related handling information.

Precautions

Review the MSDS carefully before use. Duro-Tak 87-2194 contains flammable solvents; eliminate all sources of ignition before use. Use with adequate ventilation; avoid breathing of vapor; minimize skin contact.

Migratory materials in some face stocks and end use substrates, e.g., vinyl films and foams, may affect performance. It is recommended that Duro-Tak 87-2194 be thoroughly tested for a particular application before large scale use is attempted.

X. RELATED PROCEEDINGS APPENDIX

None.